STUDY ON FIXED DOSE COMBINATION (POLYPILL) FOR CVD PREVENTION

A dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032

In partial fulfilment of the requirements for the award of degree of

MASTER OF PHARMACY
IN
PHARMACY PRACTICE

Submitted by

Reg. No. 261240208

Under the guidance of

Dr.K.Sattanathan, M.Pharm.,Ph.D.,

Department of Pharmacy Practice
J.K.K. Nattraja College of Pharmacy
Kumarapalayam-638183. Tamil Nadu

April-2014

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled "**Study on fixed dose combination (Polypill) for CVD prevention"** submitted by the student bearing [**Reg. No: 261240208]** to "**The Tamil Nadu Dr. M.G.R. Medical University**", Chennai, in partial fulfillment for the award of Degree of **Master of Pharmacy** in **Pharmacy Practice** was evaluated by us during the examination held on……..…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the dissertation **"Study on fixed dose combination (Polypill) for CVD prevention",** is a bonafide work done by [**Reg.No.261240208] J.K.K. Nataraja College of Pharmacy**, in partial fulfillment of the University rules and regulations for award of **Master of Pharmacy** in **Pharmacy Practice** under my guidance and supervision during the academic year 2013-14.

Dr.K.Sattanathan. M.Pharm., Ph.D
Guide

N.Venkateswaramurthy. M.Pharm.
HOD

Dr.R.Sambath Kumar.M.Pharm.,Ph.D
Principal

CERTIFICATE

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Dr.R.Sambath Kumar M.Pharm., Ph.D
Principal,
J.K.K. Nattraja College of Pharmacy.
Kumarapalayam-638 183

Place: Komarapalayam
Date :

CERTIFICATE

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Place: Kumarapalayam
Date :

Dr.K.Sattanathan, M.pharm,PhD.,
Professor,
Department of Pharmacy Practice,
J.K.K. Nattraja College of Pharmacy,
Komarapalayam-638 183.
Tamil Nadu

DECLARATION

I do hereby declared that the dissertation **"Study on fixed dose combination (Polypill) for CVD prevention",** submitted to "**The Tamil Nadu Dr.M.G.R Medical University"**, Chennai, for the partial fulfillment of the degree of **Master of Pharmacy** in **Pharmacy Practice,** It is a bonafide research work has been carried out by me during the academic year 2013-2014, under the guidance and supervision of **Mr.K.Sattanathan., M.Pharm.Ph.D.,** Professor, Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam .

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma ,associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **Syed Hussain Asaf**

Date: **Reg.no.261240208**

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Dedication

I dedicate this work to the people in my life that I appreciate and love more than words can say:
My parents, teachers and my friends for their unconditional love, sacrifices, encouragements, supports and “patience”.

ACKNOWLEDGEMENTS

I express whole my sincere thanks to my guide **Dr.K.Sattanathan.M.Pharm.,Ph.D.,** Professor of Department of Pharmacy Practice, for suggesting solution to problems faced by me and providing indispensable guidance, tremendous encouragement at each and every step of this dissertation work. Without his critical advice and deep-rooted knowledge, this work would not have been a reality.

I am proud to dedicate my deep sense of gratitude to the founder, (Late) Thiru **J.K.K. Nattraja Chettiar,** providing us the historical institution to study.

My sincere thanks and respectful regards to our reverent Chairperson **Smt. N. Sendamaraai, B.Com.,** Managing Director **Mr. S. Omm Sharravana, B.Com., LLB.,** and Executive Director **Mr. S. Omm Singarravel, B.E., M.S.,** J.K.K. Nattraja Educational Institutions, Komarapalayam for their blessings, encouragement and support at all times.

It is most pleasant duty to thank our beloved Principal **Dr. R. SambathKumar, M.Pharm., Ph.D.,** J.K.K.Nattraja College of Pharmacy, Komarapalayam for ensuring all the facilities were made available to me for the smooth running of this project.

My sincere thanks to **Mr**. **N. Venkateswaramurthy, M.Pharm.,** Professor and Head, Department of Pharmacy Practice. **Mrs. K. Krishna Veni, M.Pharm.,** Lecturer, Department of Pharmacy Practice, **Mrs. Christy John, M.Pharm.,** Lecturer, Department of Pharmacy Practice **Dr. K. Sattanathan, M.Pharm., Ph.D.,** Lecturer Department of pharmacy

practice**,Kavitha., M.Pharm**.**,** Lecturer, Department of Pharmacy Practice,and **Kameswaran.,M.Pharm.,** Lecturer, Department of Pharmacy Practice for their help during my project.

It is my privilege to express deepest sense of gratitude toward **Dr. R. Shanmugasundaram, M.Pharm., Ph.D.,** Professor & Vice Principal, Department of Pharmacology, **Mr. V. Rajesh, M.Pharm., Mr. C. Sridharan, M.Pharm.,** Lecturer, Department of Pharmacology, **Mr. S. Venkatesh, M.Pharm.,** Lecturer, Department of Pharmacology for their valuable suggestions during my project work.

My sincere thanks to **Mr. R. Sambath Kumar M.Pharm., Ph.D.,** Professor and Head, Department of Pharmaceutics **Mrs. S. Bhama, M.Pharm.,** Assistant Professor, **Dr. S.K. Senthilkumar, M.Pharm., Ph.D.,** Assistant Professor, **Mr. R. Kanagasabai, B. Pharm. M.Tech.,** Assistant Professor, **Mr. K. Jaganathan, M.Pharm.,** Lecturer, Department of Pharmaceutics, **Mr. C. Kannan M.Pharm.,** Lecturer, Department of Pharmaceutics and **Mr. Kamalakannan M.Pharm.,** Lecturer, Department of pharmaceutics for their valuable help during my project.

My sincere thanks to **Mr. M. Vijayabaskaran**, **M.Pharm.,** Assistant Professor and head Department of Pharmaceutical chemistry, **Mr. S.V. Arunachalam, M.Pharm.,** Lecturer, Department of Pharmaceutical chemistry, **Mrs. S. Gomathi, M.Pharm.,** Lecturer, Department of Pharmaceutical chemistry and **Mrs. S. Vasuki, M.Pharm.,** Lecturer, Department of Pharmaceutical chemistry, for their valuable suggestions and inspiration.

My sincere thanks to **Mr. V. Sekar, M.Pharm.,** Professor and Head, Department of Analysis, **Mr. M. Senthilraja, M.Pharm.,** Assistant Professor, and **Mr. S. Jayaseelan, M.Pharm.,** Assistant Professor, Department of Pharmaceutical Analysis for their valuable suggestions.

My sincere thanks to **Dr. N. Mahadevan, M.Pharm., Ph.D.,** Professor and Head, Department of Pharmacognosy, **Mr. P. Balasubramaniam, M.Pharm.,** Lecturer, Department of Pharmacognosy, and **Meena Prabha.,M.Pharm.,** Lecturer, Department of Pharmacognosy for their valuable suggestions during my project work.

. I greatly acknowledge the help rendered by **Mrs. K. Rani,** Office Superintendent, **Miss. Prabha, Mrs. V. Gandhimathi, M.A., M.L.I.S.,** Librarian, and **Mrs. S. Jayakala, B.A., B.L.I.S.,** Asst. Librarian for their co-operation.

"Friends are in need are friends indeed", I am really thankful and grateful to beloved friends**, C.Sam pushparaj, Sumitha, N.Malaravan, A.Sivakumar** for their constant encouragement and moral support throughout my course and stay.

I owe my thanks to all the technical and non-technical staff members of the institute for their precious assistance and help.

Last, but nevertheless, I am thankful to my lovable parents and all my friends for their co-operation, encouragement and help extended to me throughout my project work.

SYED HUSSAIN ASAF

Reg.No:261240208

INTRODUCTION

An epidemic of Cardiovascular disease (CVD) is a predicted in the Indian subcontinent as a result of change in demographics and lifestyle and poor childhood nutrition impacting on disease in adult life.[1, 2] In contrast to the west the prevalence of ischemic heart disease in India has been steadily increasing over the last two decades, from around 1-4% to over 10%, these figures are based on survey data but supported by clinical impression.[3, 4, 5] the prevalence in rural areas is about half that of urban populations.[6] It is predicted that CVD will be the leading cause of death in india in years to come

Asian Indians have higher prevalence of premature ischemic heart disease than Europeans, Chinese and Malayas[5]; this is likely to be influenced by conventional risk factors such as smoking, blood pressure and cholesterol levels plus an increasing prevalence of insulin resistance and other metabolic abnormalities.[6]

Reducing CVD and the impact of the epidemic will require extensive public health strategies at the population and individual levels. The lack of facilities for diagnosis and treatment of CVD and the cost of treatment mean that large sections of the Indian populations have poor access to both prevention and treatment,[3] one cost effective approach, which could achieve substantial benefits within a few years, is provision of combined Cardiovascular (CV) medication to those at highest risk.

Indications for three classes of treatment (antiplatelet therapy, blood pressure lowering and cholesterol lowering) exist among people at highest risk of CVD. Individuals with symptomatic coronary or Cerebrovascular Disease or diabetes with complications have over a 20% risk of a CV event in the next 5 years.[9]

These patient groups are at the highest risk of CVD and account for about half of all CV deaths and hospitalizations.[10] International guide lines now recommend almost all such high risk individuals receive treatment with each of three classes of CV medication namely antiplatelet, blood pressure lowering and cholesterol lowering therapies.[9, 11, 17] The evidence base for these recommendations is one of the most extensive in medical care ,with many tens of thousands participants in major trials of each class of treatment.[12]

Land mark trails recently published, including the heart protection study[18] and progress [19] definitely show that these treatments should be provided largely irrespective of baseline factor levels or concomitant treatments. These and other large scale trails such as hope[20] and lipid[21, 22] as well as overuse of antiplatelet therapy[23] show that the benefits extended to all major subgroups eg: defined by age sex and type of vascular disease thus there unequivocal evidence that virtually all people with established vascular disease or who are otherwise at high risk would benefit from treatment with antiplatelet, blood pressure and cholesterol lowering therapies.[24, 25]

A cross sectional survey of approximately 1,100 residents of two areas in Urban South India found that of the 47 individuals with Definite Coronary Artery Disease only 23.4% of these were on therapy with blood pressure lowering drugs (with only half receiving β–blockers) and (2%) was on a lipid lowering drugs.[5] Comparison of 71 tertiary and secondary centers over India with data over 4,000 acute coronary syndrome patients found that at 30 days nearly all were receiving antiplatelet agents but less than half were prescribed β –blockers(60% and 51%).[28] similarly a study of acute myocardial infarction (MI) showed that Thrombolysis, β-blockers and Angiotensin-converting enzyme-I(ACE-I)inhibitors, were used in 674(63%), 596(47%) and 413(38%) respectively of 1072 patients.[27]

EUROASPIRE II surveyed CHD patients in across Europe found good levels of antiplatelet use, a range of β-blocker use between countries (47-88%) and persistent low use of statins (40-60%), although this represented a substantial increase in statin use since the previous survey four year earlier.[40] A British survey showed that less than half of women with a history of myocardial infarction or stroke were taking antiplatelet medication and only one in five were receiving a statin[31] a review in Italy demonstrated that a third of patients with a history of stroke or transient ischemic attack were not on antiplatelet therapy.[32]A study on patients with established coronary disease in New Zealand found that (personal communication, A Kerr). Only 11% were receiving lipid lowering, antiplatelet therapy, an ACE inhibitor and a β-blocker (i.e. current guideline recommendations). In a recent Australian general practice study of over 10,000 participants (professor Chris Reid personal communication) only about one third of patients were receiving guideline – recommended combination of medications.

Potential to improve adherence with fixed dose combination(polypill) medication

The reasons for treatment gaps are complex and likely to include resistance (on the part of both physicians and patients) to the cost, complexity and stigmatization of prescribing for or more separate CV medications and resultant low adherence, as well as poor dissemination and uptake of guidelines .Including dosing more than one day .[35] Cost can be an important factor[36, 37] and patients can delay or omit doses[38] and not fill prescreptions.[37] As strategies for cost reduction. Despite widespread perceptions, placebo–controlled trails show that non–adherence for common CV medications are rarely due to pharmacological side effects. In long term trials of low dose aspirin, blood pressure and cholesterol lowering, Only 1-3% percent of people stopped medication due to side effects attributable to the medicines, but a further 10-25% stopped for other reasons. For example, in PROGRESS 13% of people in the active group stopped all treatment over 4 years, but so did 11% in the placebo group.[19]

Simple, low cost combination pills may represent an important opportunity for improving provision and adherence of effective CV medications. Encouraging but inconclusive results were seen in a systematic review (Connor et al, in press[39]) of randomized trials assessing the effect of combination pills and unit-of-use packing compared with the same medications presented as separate pills. Despite very small sample sizes in many of the trials (less than half had over 100 participants), tends to improvements in adherence and on clinical outcomes were seen in 11 of 14 trials including 3 trails of hypertension treatment and one study of combination packing conducted in people with diabetes in New Zealand.[40]

A major cost-effectiveness analysis conducted for the World Health Report clearly showed that absolute risk based combination treatment is more cost- effective then threshold-based unifactoral approaches (e.g.hypertension treatment) in all world regions and age and sex groups.[41] Indeed this strategy appears particularly attractive in terms of dollars per disability-adjusted life year (DALY) averted compared to a wide range of preventive activities and have the potential to substantially reduce CVD at the population level. A strategy of non-personal interventions such as salt reduction in food and use of combination treatment based on absolute risk has the potential to reduce CV events by more than 50%.[41]

Hypertension: [42]

This is called as high blood pressure, is a medical condition in which the blood pressure is chronically elevated.

Types of Hypertension:

Physicians classify the different kinds of hypertension based on their causes and characteristics.

1. Primary (essential) hypertension.
2. Secondary hypertension.

Primary (essential) Hypertension:

It indicates that no specific medical cause can be found to explain patient's condition. About 95% of hypertension is essential hypertension. Primary hypertension is caused by variety of factors.

Isolated Systolic Hypertension:

This is one of the types of primary hypertension. As people age their arteries tend to lose elasticity and become less able to accommodate blood surges. The damage created in the vessel lining when blood flow through the arteries at high pressure can accelerate plaque build up, this lead to atherosclerosis this can elevate systolic blood pressure, while diastolic blood pressure stays in the normal range. This is called isolated systolic blood pressure.

Secondary Hypertension:

It is indicates that the high blood pressure is a result of secondary to another condition such as kidney disease or tumors (Adrenal adenoma or Pheochromocytoma).

Causes of secondary hypertension are:

- Renal artery stenosis.
- Hyperaldosteronism.
- Hyperthyroidism.
- Pheochromocytoma.
- Caushing's syndrome and Coarctation of the aorta.

Blood pressure Measurement: [43]

Blood pressure is measured in the form of two numbers, namely, the systolic and the diastolic blood pressure. It is written as 120/80, where 120 is the systolic blood pressure and 80 is the diastolic blood pressure. Systolic pressure is the pressure of the blood when heart beats. This is the highest pressure exerted by the blood. Diastolic pressure is the pressure of the blood when the heart rests between beats this is the lowest pressure exerted by the blood.

There are two ways of measuring blood pressure.

1) The Auscultatory method.
2) The Oscillometric method.

1. Auscultatory method:

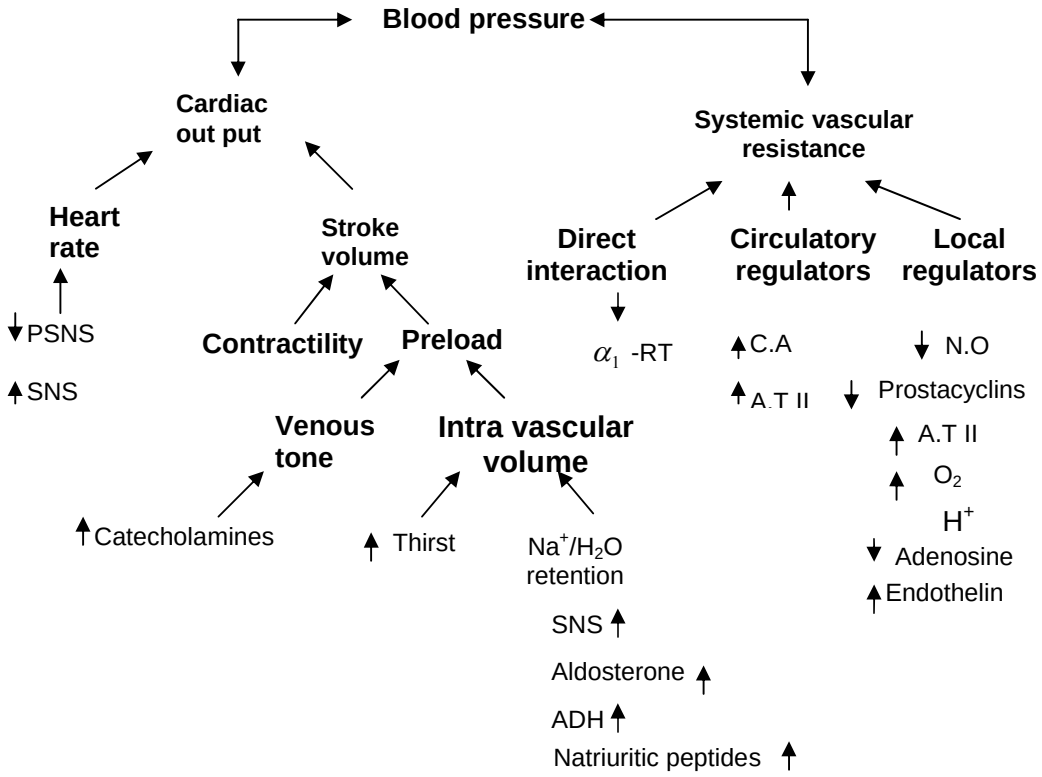
In this method, a Stethoscope and a sphygmomanometer are used. In this method, an inflatable cuff is placed around the upper arm, at roughly the same vertical height as the heart. The cuff is attached to mercury. The cuff is inflated manually by squeezing a rubber bulb repeatedly until the artery is completely occluded.

The pressure in the cuff is slowly reduced. A whooshing or pounding sound is heard. The pressure at this point is called systolic pressure. Then the pressure in the cuff is further reduced, till no sound is heard. The pressure at this point is called diastolic blood pressure. Both these pressures are record to find out the accurate blood pressure.

2. Osillometric method:

This method is similar to the auscultatory method functionally. It is used in long term measurement as well as in clinical practice. The cuff in this type of monometer comes with an electronic pressure sensor fitted in the cuff to detect the blood flow. In this method, the mercury manometer is fitted on the wrist, elevated to the height of the heart, though the upper arm is always preferred. The cuff is inflated and released by an electrically operated pump, which then gives out a numerical read out of the blood pressure. Oscillometric measurement does not require much skill and is easy to use by even non trained staff and patient themselves.

Regulation of blood pressure: [44]



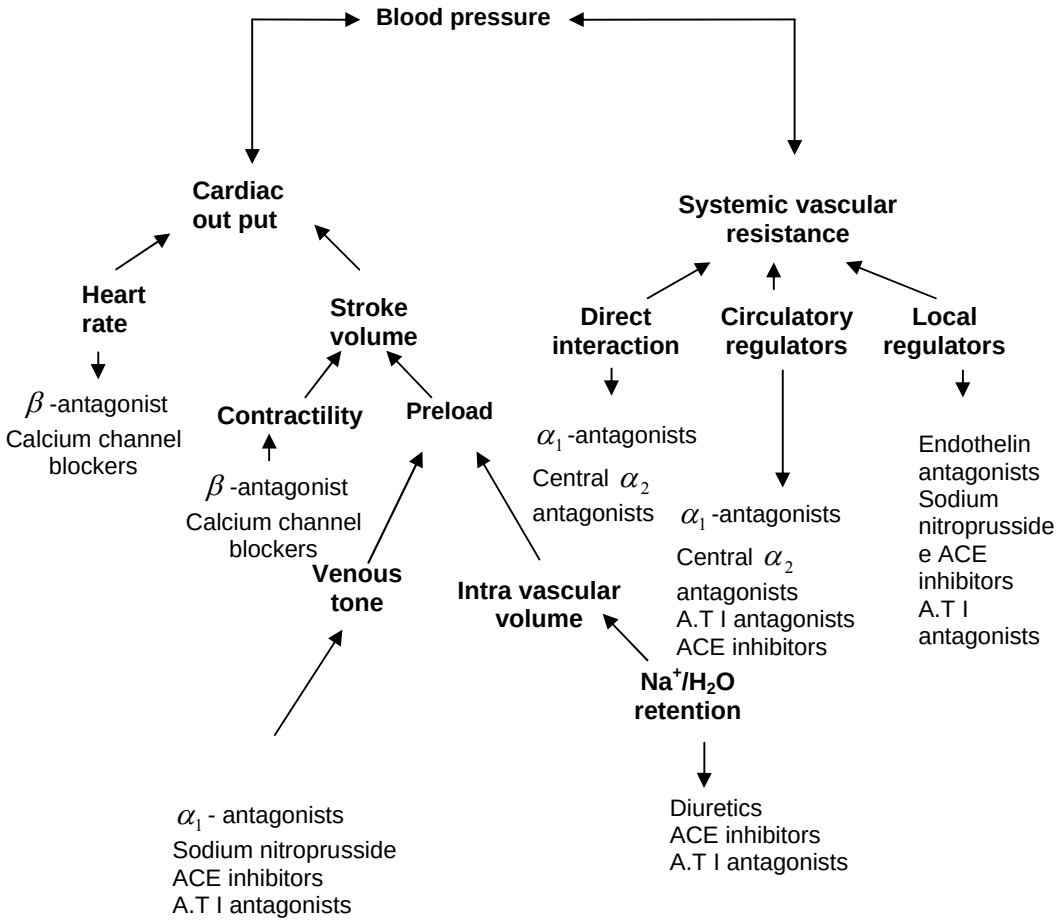
Classification of Hypertension for Adults according to JNC-VII[45]:

Condition	Systolic Blood pressure	Diastolic Blood pressure
Normal	< 120 mm of Hg and	< 80 mm of Hg
Prehypertension	120-139 mm of Hg (or)	80-89 mm of Hg
Hypertension Stage-I (Moderate)	140-159 mm of Hg (or)	90-99 mm of Hg
Hypertension Stage-II (severe)	≥ 160 mm of Hg (or)	≥ 100 mm of Hg

Pharmacological treatment of Hypertension:[46]

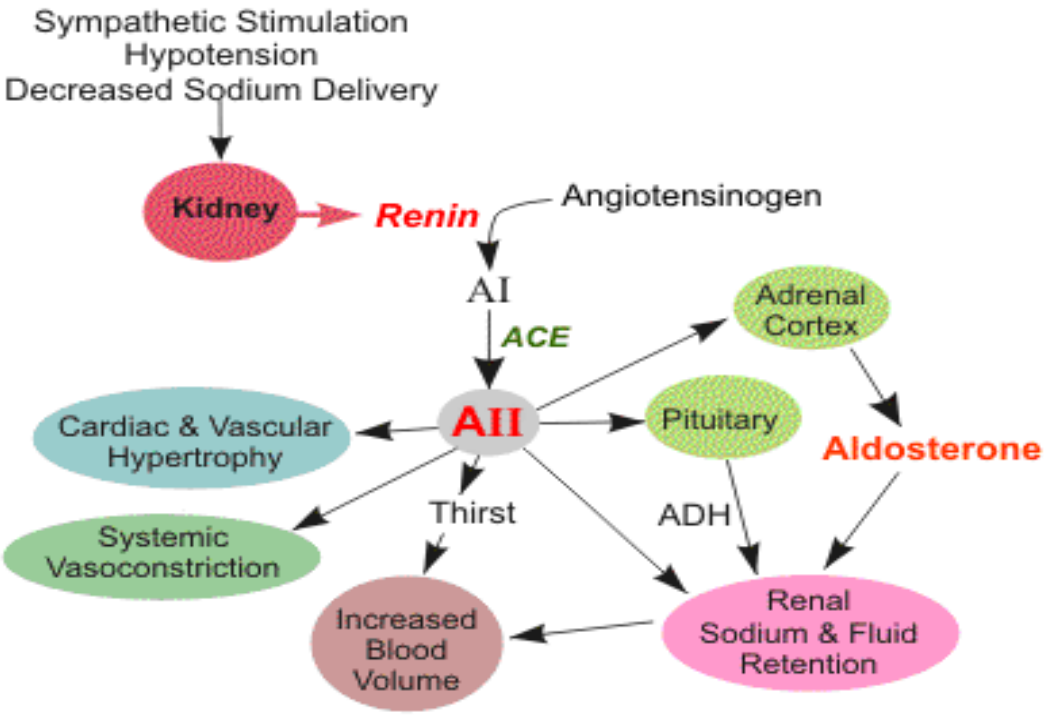
S.No.	Category	Drug classification	Drugs
1.	Diuretics	a)Thiazide diuretics b)Loop diuretics c) K^+-sparing diuretics	Chlorthiazide, Hydrochlorothiazide Furosemide, Ethacrynic acid, Torsemide, Amiloride, Spiranolactone, Triamterene.
2.	Sympatholytics	a) CNS sympathetic out flow blockers. b) Ganglionic blockers c) Post Ganglionic adrenergic nerve terminal antagonists d) α_1 -Adrenergic blockers e) β_1 -Adrenergic blockers	Clonidine, Methyldopa. Trimethophan, Hexamethonium Gunethidine, Reserpine Prazosin , Terazosin(selective) Phentolamine, Phenoxy-benzamine (Non selective) Atenolol, Timolol, Pindolol
3.	Vasodilators	a) Ca^{2+} channel blockers. b) K^+ channel openers. c) Arteriolar Venular vasodilators	Nefidipine, Amilodpine Minoxidil, Hydralazine. Sodium nitroprusside.
4.	RAAS inhibitors	a) ACE inhibitors b) Renin inhibitors C) AT1 antagonists	Captopril, Ramipril, Enalapril, Lisinopril. B-blockers. Losartan, Valsartan

Mechanism action of Antihypertensive drugs: [46]



Renin-Angiotensin Aldosterone System: [47]

Renin-Angiotensin-Aldosterone System (RAAS) plays an important role in regulating blood volume and systemic vascular resistance, which together influence cardiac output and arterial pressure.



Renin is a proteolytic enzyme that is released from the kidneys, its release is stimulated by the:

- Sympathetic nerve activation (acting via β_1 adrenoceptors).
- Renal artery Hypotension (caused by Systemic Hypotension or Renal artery stenosis).
- Decreased Sodium delivery to the distal tubules of the kidney.

When Renin is released in to the blood, it acts upon a circulating substrate, Angiotensinogen that undergoes Proteolytic cleavage to form the Decapeptide Angiotensin I. Vascular endothelium, particularly in the lungs, has an enzyme, Angiotensin converting enzyme (ACE) that cleaves of two amino acids to form the Octapeptide, Angiotensin II (AII).

Functions of Angiotensin II:

- Constricts resistance vessels (via AII, AT_1 receptors) there by increasing systemic vascular resistance and arterial pressure.
- Act on the adrenal cortex to release Aldosterone, which in turn acts on the kidneys to increase sodium and fluid retention.
- Stimulates the release of vasopressin (anti diuretic hormone, ADH) from the Posterior pituitary, which increases fluid retention by the kidneys.
- Stimulates thirst centers within the brain.
- Facilitates Norepinephrine release from sympathetic nerve endings and inhibits Norepinephrine re-uptake by nerve endings, there by enhancing sympathetic adrenergic function.
- Stimulates cardiac hypertrophy and vascular hypertrophy.

Manipulation of this pathway is very important in treating hypertension. ACE inhibitors, AII receptor blockers and Aldosterone receptor blockers are used to decrease arterial pressure, ventricular after load, blood volume and hence ventricular preload, as well as inhibit and reverse cardiac and vascular hypertrophy.

Adverse effects of ACE inhibitors: [48]

Common adverse drug reactions:

- Hypotension,
- Cough,
- Hyperkalemia
- Headache
- Dizziness
- Fatigue
- Nausea
- Renal impairment

A persistent Dry cough is a relatively common adverse effect believed to be associated with the increases in Bradykinin levels produced by ACE inhibitors.
Rash and taste disturbances are infrequent with most ACE inhibitors.

Renal impairment is a significant adverse effect of all ACE inhibitors. The reason for this is still unknown. ACE inhibitors may cause Hyperkalemia. Suppression of Angiotensin II leads to a decrease in Aldosterone levels. Since Aldosterone is responsible for increasing the excretion of potassium, ACE inhibitors ultimately cause retention of potassium. A severe allergic reaction can occur that rarely can affect the bowel wall and secondarily cause abdominal pain. This "Anaphylactic" reaction is very rare as well. Some patients develop Angioedema due to increased Bradykinin levels.

Dyslipidemia (Hyperlipidemia)[49]:

It is defend as an abnormality in lipid metabolism leads to increased elevation of disorder of lipoprotein metabolism, including lipoprotein over production or deficiency. Dyslipidemia may be manifested by elevation of the total cholesterol, the "bad" low-density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and a decrease in the "good" high-density lipoprotein (HDL) cholesterol concentration in the blood.

Dyslipidemia can be divided into,

1. Primary Hyperlipidemia
2. Secondary Hyperlipidemia

Primary Hyperlipidemia:

S.No.	Disease	Characteristic lipid profile
1.	**Primary Hypercholesterolemia**	
a.	Familial hypercholesterolemia	↑↑LDL.
b.	Familial defective ApoB100	↑↑LDL.
c.	Autosomal recessive hypercholesterolemia	↑LDL.
d.	Polygenic Hypercholesterolemia	↑cholesterol
2.	**Primary Hypertriglyceridemia**	
a.	Familial Hypertriglyceridemia	↑TG, ↑VLDL, ↓HDL.
b.	Familial lipoprotein lipase deficiency	↑↑ TG
c.	Apo CII deficiency	↑↑ TG
3.	**Mixed Hyperlipidemia**	
a.	Familial combined Hyperlipidemia	↑TG, ↑LDL, ↓HDL
b.	Familial Dysbetalipoproteinemia	↑TG, ↑LDL, ↑cholesterol, ↑remnants
4.	**Disorders of HDL metabolism**	
a.	Polygenic Low HDL	↓HDL
b.	Familial Hypoalphalipoproteinemia	↓HDL
c.	Familial Apo-AI deficiency	↓HDL
d.	Tangier deficiency	
e.	Fisheye disease	↓HDL
f.	LCAT deficiency	↓HDL

Secondary Hyperlipidemia:

Secondary hypertension is attributed to some other reason like, Diabetes mellitus, Hypothyroidism, Chronic Renal failure, Glucagon storage disease, stress, etc.,

Optimal, Borderline, and high levels for each component: [50]

SOURCE: National Cholesterol Education Program (NCEP) Adult Treatment panel III (ATPIII) approach to Dyslipidemia.

ELIMENT	OPTIMAL	BORDERLINE	HIGH RISK
LDL cholesterol	<100	130-159	160+
HDL cholesterol	>60	35-45	<35
Triglycerides	<150	150-199	>200
Total cholesterol	<200	200-239	>240
Cholesterol to HDL ratio	<4	5	>6

Lipoproteins and Dyslipidemia: [51]

Lipoproteins are macromolecular structures aggregates that transport Triglycerides and Cholesterol in the blood. Circulating lipoproteins can be differentiated on the basis of Density, size, and protein content

They are:

- Chyolomicrons (CM)
- Very low density Lipoproteins (VLDL)
- Intermediate Low Density Lipoproteins (IDL)
- Low Density Lipoproteins (LDL)
- High Density Lipoproteins (HDL)

S. NO.	Parameters	CM	VLDL	IDL	LDL	HDL
1	**Density (g/ml)**	<0.95	0.95-1.006	1.006-1.019	1.019-1.063	1.063-1.21
2.	**Diameter (nm)**	75-1200	30-80	25-35	18-25	5-12
3.	**Total lipid (%wt.)**	98	90	82	75	67
4.	**Composition(% dry wt.)**					
a.	**Protein**	2	10	18	25	33
b.	**Triglycerides**	83	50	31	9	8
c.	**Unesterified cholesterol and cholesterol esters**	7	22	29	45	30
5.	**Phospholipids (%wt. Lipid)**	7	18	22	21	29
6.	**Major Apolipoprotiens**	B48, AI, AIV, E, CI, CII, CIII	B100, E,CI, CII,CIII	B100, E, CI, CII, CIII	B100	AI, AII, E, CI, CII, CIII

Diagnosis:

Serum lipid profile is used for the measuring total cholesterol, TG, and HDL-cholesterol and calculated LDL-cholesterol and VLDL.

Treatment: [52]

Goals for Lipid Lowering were established in the National cholesterol education program adult treatment panel III (ATP). Guidelines which provide target LDL levels.

Treatment strategies:

1. Dietary therapy
2. Exercise and stress reduction.
3. Drug therapy

a. Statins- HMG COA reductase inhibitors:

Lovastatin
Simvastatin
Pravastatin
Atorvastatin
Rusavastatin

b. Bile acids Binding resins:

Cholestyramine
Colespitol

c. Fibrates and derivatives :

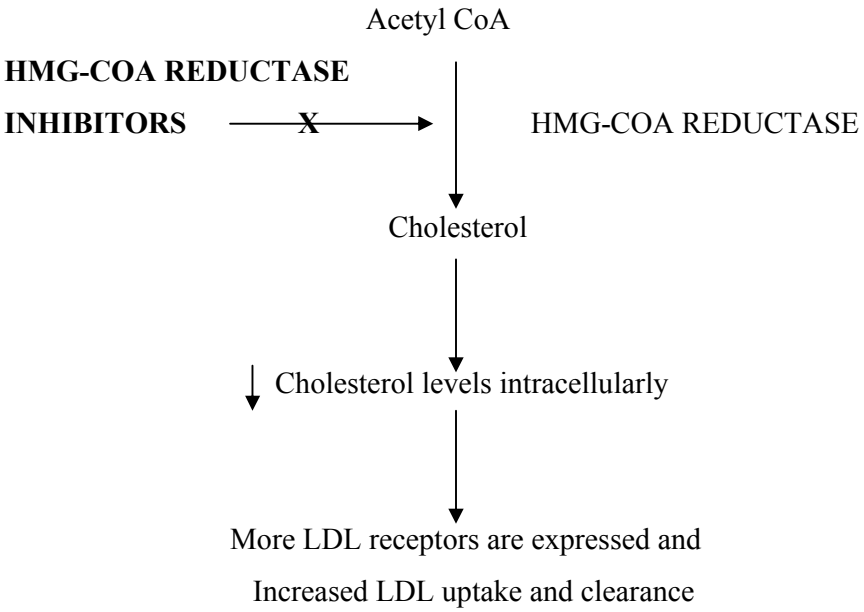
Benzfibrate
Clofibrate
Gemfibrozil
Ciprofibrate

d. Nicotinic acid

e. Fish oil

f. Cholesterol absorption inhibitor: Ezeimibe

Mechanism of action of statins:



ADVERSE EFFECTS OF STATINS: [52]

"Muscle problems are the best known of statin drugs' adverse side effects," said Golomb. "But cognitive problems and peripheral neuropathy, or pain or numbness in the extremities like fingers and toes, are also widely reported." A spectrum of other problems, ranging from blood glucose elevations to tendon problems, can also occur as side effects from statins.

LITERATURE REVIEW

Raia JJ, et al., Done comparative review on angiotensin-converting inhibitors, are capable of lowering blood pressure primarily by promoting vasodilation and reducing intravascular fluid volume. Captopril, is an active ACE inhibitor in its orally absorbable parent form. In contrast, enalapril must be deesterified in the liver to the metabolite enalaprilat in order to inhibit the converting enzyme; this account for its delayed onset of action. Lisinopril does not require metabolic activation to be effective; however, a slow and incomplete absorption pattern explains the delay in onset of activity.[53]

Tendera M, et al., studied role of antiplatelet drugs in the prevention of cardiovascular events in variety of clinical conditions, such as myocardial infarction, raise stroke and cardiovascular death. Both European and American guidelines recommend the use of antiplatelet drugs in patients with established coronary disease and other atherosclerotic disease. In high risk patients, such as those with post acute myocardial infarction (AMI), ischemic stroke or transient ischemic attack, and patients with stable or unstable angina, peripheral arterial occlusive disease or atrial fibrillation, antiplatelet treatment may reduce the risk of a serious cardiovascular event by approximately 25%, including reduction of non-fatal myocardial infarction by 1/6, non fatal stroke by 1/4 and cardiovascular death by1/6. Aspirin has been studied and used most extensively. It may exert its beneficial effect not only by acting on platelets, but also by other mechanisms, such as preventing thromboxane A2 (TXA2) induced vasoconstriction or reducing inflammation. Experimental data show that low dose aspirin may suppress vascular inflammation and thereby increase the stability of atherosclerotic plaque.[54]

Teo KK, et al., evaluated long term treatment with angiotensin converting enzyme (ACE I) inhibitors in the presence or absence of aspirin. They used the peto-yusuf method to undertake a systemic overview of data for 22060 patients from six long term randomised trials of ACE inhibitors to assess whether aspirin altered the effects of ACE inhibitor therapy on major clinical outcomes (composite of death, myocardial infarction, stroke, hospital admission for CHF, or revascularization). ACE inhibitor therapy significantly reduced the risk of the major clinical outcomes by 22%

($p<0.0001$), with clear reductions in risk both among those receiving aspirin at baseline (odd ratio 0.80, 99% CI 0.73 - 0.88) and those who were not (0.71, 99% CI 0.62 - 0.81).[55]

Oates JA. Studied that is Antagonism of Antihypertensive Drug Therapy by Non steroidal Anti-inflammatory drugs. Certain non steroidal anti-inflammatory drugs antagonise the action of antihypertensive therapy. Indomethacin has been shown to abrogate the antihypertensive effect of beta-adrenergic receptor blockers, diuretics, Angitensin converting enzyme inhibitors and several antihypertensive drug combinations and the accumulated evidence on Piroxicam indicates that it also raises arterial pressure in treated patients. In contrast, Sulindac and aspirin do not reverse the effects of antihypertensive drugs and currently available data indicate that they are the safest Cyclooxygenase inhibitors for use in hypertensive patients.[56]

Musial J, et al., evaluated treatment with Simvastatin and low dose aspirin depress thrombin generation in patients with coronary heart disease and borderline–high cholesterol levels. They investigated whether in patients with borderline–high cholesterol levels who have been already taking aspirin, additional treatment with Simvastatin would affect thrombin generation. Seven day treatment with low dose aspirin decreased thrombin generation exvivo only in patients with total cholesterol ≤ 5.2 mmol/l, in patients with higher cholesterol levels aspirin had no effect. In these patients, already taking low dose aspirin, additional three month Simvastatin treatment resulted in a reduction of thrombin generation. This demonstrates that low–dose aspirin depress thrombin generation only in subjects with desirable blood cholesterol levels, while in others, with borderline–high cholesterol, thrombin formation is being reduced following addition of Simvastatin.[57]

Sposito AC, et al., studied on additional reduction in blood pressure after cholesterol-lowering treatment by statins (Lovastatin or Pravastatin) in Hypercholesterolemic patients using angiotensin–converting enzyme inhibitors (Enalapril or Lisinopril). Blood pressure reduction was compared between patients receiving angiotensin converting enzyme inhibitors alone and patients receiving these medications plus statins after three months of dietary intervention. Although BP was similarly reduced at 4^{th} week, the statin treated group had a greater reduction in BP and cholesterol

lowering with statins and Angiotensin – Converting enzyme inhibitor treatment for hypertensive patients.[58]

Paoletti R, et al., studied on pharmacological interactions of statins. HMG-CoA reductase inhibitors are effective in reducing the risk of coronary events and are generally very well tolerated, these are biotransformed in the liver primarily by cytochrome P450(CYP)3A4 clinical experience has shown that the risk of adverse effects, such as myopathy, myositis, and rhabdomyolysis have been reported. In some statins may have lower adverse drug interaction potential then others, which is an important determinant of safety during long term therapy.[59]

Skoularigis J, et al., evaluated efficacy of low dose (12.5 to 25mg) hydrochlorothiazide was evaluated by ambulatory blood pressure monitoring in 19 mild to moderate hypertensive (mean 12-h diastolic BP>or 90 mm hg and <115 mm Hg) south African black patients. After a 3 week placebo run–in period, HCTZ was administered for 8 weeks as Monotherapy. The mean day time ABPM was only 32% patients achieved BP control. 24-h BP load fell from 69% at baseline, to 53% with 12.5 mg HCTZ and 47% with 25 mg HCTZ daily there were no side effects but the increase of HCTZ to 25 mg daily was followed by adverse changes in serum potassium levels. It is concluded that low dose of HCTZ Monotherapy has only a moderate effect on the BP control. And 24-h BP loads while the higher 25 mg dose is associated with significant decrease in serum potassium level.[60]

Galan L, et al., studied on cardiac cellular actions of hydrochlorothiazide. Long term treatment, Thiazide diuretics such as Hydrochlorothiazide lower blood pressure by decreasing peripheral vascular resistance rather than by their diuretic effect. This action has been attributed to the opening of Ca^{2+} activated K^{+} channels in vascular smooth muscle cells.[61]

Shaw E, et al., Discussed on factors associated with non compliance of patients taking antihypertensive medications, poor adherence to drug therapy decreases the effectiveness of antihypertensive treatment patient must take more than 80% of their antihypertensive drugs to maintain the adequate blood pressure control. Pilot study was conducted in which a questionnaire and contributing was devised and administered to a random sample of 243 hypertensive patients of the adult ambulatory

care clinic at Methodist Hospital of Indiana. Ninety eight patients completed the telephone survey. Demographic review was obtained from chart review.[62]

The results indicated that 30-46% of the patients were non compliant with their antihypertensive drug regimens. Factors found to be associated non compliance were employment (P=0.0077), use of home remedies (P=0.0043), age (P=0.0165), experience of the side effects (P=0.0051), level of concern with missed doses (P=0.0043 and cost (P=0.014). The incidence of non compliance in this pilot sample is lower than the estimated 50% noncompliance rate of published data.

Gradman AH, et al., evolving strategies for the use of combination therapy in hypertension, two thirds of patients with hypertension require more then one drug to achieve goal blood pressure some combinations exhibit side effect neutralization in which side effects associated with one drug are neutralized by a second agent. Fixed dose combinations reduce the no of pills and simplifying the treatment regimen. Because volume overload is common, low dose diuretics are often included in drug combinations. Combination of diuretics with potassium sparing diuretics, Angiotensin Converting Enzyme Inhibitors, Angiotensin receptor blockers, and b-blockers are use full in treating large segments of the hypertension population.[63]

Waeber B, et al., studied on combined treatment with Captopril, Hydrochlorothiazide and Pravastatin in dyslipidemic hypertensive patients. Design: the patient were followed for 16 weeks and asked to comply with a lipid lowering diet for the whole period. Captopril 50mg/once daily was administered alone for the first 4 weeks .Hydrochlorothiazide, 25 mg/day, was added after 4weeks if required. Pravastatin (20mg/day) was started at the 8th week of the study and its dose was doubled 4 weeks later if needed. Determination of blood pressure, circulating levels of Total Cholesterol, HDL-cholesterol and Triglycerides, and blood chemistry for safety monitoring. Results: At the end of the trail 75.1% of patients of their diastolic blood pressure $\leq$90 mmHg and 43.5% a total cholesterol is <6.5 mmol/l the overall incidence of adverse events was 21.7% leading to withdrawal in 10.9% of the total number of patients. The combined treatment had no deleterious effect on safety variables. Conclusion: Captopril, Hydrochlorothiazide and Pravastatin are effective and well tolerated medications to treat dyslipidemic hypertensive patients.[64]

SCOPE OF THE STUDY

The world Health Report showed the substantial and previously under-estimated impact of known risks, such as high blood pressure and cholesterol, in causing cardiovascular disease. More than half of all cardiovascular disease burdens can be attributed to blood pressure and cholesterol they are leading risks to health in all developed countries and are increasingly important in developing countries.[65]

The reasons for treatment gaps are complex and likely to include resistance (on the part of both physicians and patients) to the cost, complexity and stigmatization of prescribing for more separate CV medications and resultant low adherence, as well as poor dissemination and uptake of guidelines. Including dosing more than one day.[35] Cost can be an important factor, [36, 37] and patients can delay or omit doses[38] and not fill prescriptions.

International guidelines now recommend almost all such high risk individuals receive treatment with each of three classes of CV medication, namely antiplatelet, blood pressure lowering and cholesterol lowering therapies.[9, 11, and 17]

A combination pill taken once daily has the ability to address many of these issues: the use of multiple drugs might be more acceptable if they were to be combined into a single pill containing four categories of drugs, for example, aspirin, two categories of antihypertensive drugs and a statin, and taken once a day. The use of single pill could well encourage patients to adhere to treatments as well as seriously reduce the cost of the drugs. The use of combination pill could be considered and evaluated in patients suffering from all other cardiovascular conditions.[66]

Interventions to lower blood pressure, serum cholesterol, and other risk factors also reduce the cardiovascular disease. Randomised trails show that drugs to lower three risk factors- low density lipoprotein (LDL) cholesterol, Blood pressure ,and platelet function (with Aspirin) reduce the incidence of cardiovascular events. A strategy to simultaneously reduce 3 cardiovascular risk factors (low density lipoprotein cholesterol, blood pressure and platelet function) has been recommended recently based on meta analysis of randomised trails and cohort studies of antihypertensive drugs and statins and a Meta analysis of 15 trails of low dose

(50-125 mg/Day) Aspirin. The formulation, which met the objectives, had a statin (for example Atorvastatin or **Simvastain**); blood pressure lowering drugs (for example, a **Thiazide,** β-blocker and an **Angiotensin converting enzyme inhibitor)**, each at half standard dose and aspirin (100mg). It was estimated that the combination would reduce MI,Stoke & cardio vascular death by 75% in secondary prevention.

Hence the company has developed a fixed dose combination of a statin (Simvastatin), an antiplatelet agent (Aspirin), an ACE-inhibitor (ramipril) and a Diuretic (Hydrochlorothiazide).[74]

OBJECTIVE

To evaluate the fixed dose combination of Simvastatin, Aspirin, Hydrochlorothiazide, ramipril and atenolol results in lowering blood pressure and cholesterol levels and improved adherence in patients with at least one Cardiovascular risk factor such as Hypertension and Dyslipidemia or Coronary Artery Disease.

Drug name - polycap
(cadila pharmaceuticals)

Aspirin - 100mg
Atenolol - 50mg
Hydrochlorthiazide - 125mg
Ramipril - 5mg
Simvastatin – 20mg

METHODOLOGY

Study Design and Setting:

The study was prospective open labeled 12 weeks. This study was conducted in KMCH Hospital Coimbatore.

Ethical considerations:

The ethical committee in the Institution approved the study process. The ethical committee will be provided with the reports and the progress.

Identification of eligible patients:

The patients under study will be included, males and females aging between 18-75 years with mild to moderate hypertension as suggested by JNC-VII [≥139/89 mm of Hg and ≤ 180/110 mm of Hg] and along with abnormal lipid profile LDL-C ≥130 mg/dl or LDL-C >100 mg/dl with CAD equivalents (CAD - Coronary artery disease will be diagnosed on patients history/ ECG/Angiogram; Coronary artery disease Equivalents are diabetes mellitus, abdominal aortic aneurism, symptomatic carotid artery disease).

Eligibility:

Inclusion criteria:

1. Adults Male or Female age 18 – 75 years.
2. Patients with at least one risk factor for cardiovascular disease namely hypertension ≥ 139/89 mm of Hg and ≤ 180/110 mm of Hg according to JNC-VII guidelines and lipid profile LDL-C ≥130 mg/dl or LDL-C >100 mg/dl with CAD Equivalents or patient with coronary artery disease or high cardiovascular risk factors. At the screening visits.

Exclusion Criteria:

The following patients will be excluded:

1. Contraindication /intolerance (e.g.Asthama, peripheral vascular disease for Atenolol) to any of the components of the combination pill.
2. The physician is of the opinion that changing a patient's medication would put the patient at risk (e.g. heart failure, high dose β - blocker required to manage anginal symptoms)
3. Acute medical conditions/surgeries
4. Medical/psychiatric conditions likely to hinder trail process
5. Lactating and pregnant women.
6. Women of reproductive age, not practicing contraception.
7. Hepatic Dysfunction
8. Renal Dysfunction.
9. Unwilling to give informed consent.

Withdrawals and Dropouts:

A subject may be withdrawn from therapy on account of development of an intolerable adverse event.

Study Medication and Dosing

The study for two combinations in tablets form,

Combination Pill			
Low Dose		**Medium Dose**	
Aspirin	100mg	Aspirin	100mg
Hydrochlorothiazide	12.5mg	Hydrochlorothiazide	12.5mg
Simvastatin	10mg	Simvastatin	20mg
Ramipril	5mg	Ramipril	10mg
Atenolol	50mg	Atenolol	50mg

Low Dose pill taken once daily increased to medium dose, if necessary after therapy of 4 weeks, if no improvement or worsening of both LDL-C or/and blood pressure (systolic/diastolic) measurements. If there is improvement in both LDL-C and BP (systolic and diastolic), keep the low dose for next 8 weeks.

All patients who develop dry irritating cough in the 1st 4 weeks of combination pill therapy shall be withdrawn from the study.

Tablets will be checked to ensure they will not exceed their expiry date at any stage of their prescription to subjects. They will then be dispensed to the patients for 12 weeks they will then be placed in number coded containers.

Methodology:

Eligible patients will have a copy of the Ethics Committee approved patient information sheet placed in the medical record. The study will be explained during the clinical consultation. After the explanation the subject will be provided the patient information sheet and Informed Consent Form (ICF). The subject will be asked to take this away with them and arrangements will be made to follow up via a telephone call. If the subject agrees to participate, they will sign the consent form with an independent person signing as a witness to this process.

In the next step, the selected patients details are maintained separately for recording the screening parameters (Blood Pressure, LDL-Cholesterol, Total Triglycerides, Heart Rate, Brief details of the patient, date of onset of study, Screening details from baseline visit to 4th visit, doses of the drugs given to the patients, Adverse reactions of the drug if any. All the adverse reactions should be follow-up either to resolution or to a point where no further improvement is expected.

Visit schedule:

The selected eligible patients who had given the ICF are subjected for screening of blood and urine samples which were sent for the baseline safety investigations.

The patients are advised to visit the Hospital in 4 visits.

Visit-1 for baseline screening (Day 1),

Visit-II in 4th week from baseline screening date,

Visit-III in 8th week from baseline screening date,

Visit-IV in the 12th week from baseline screening date.

Screening visit:

Only those patients willing to give informed consent will be recruited. The patient will be assessed for presence of inclusion and absence of exclusion criteria. Selected patients will have their serum and urine samples sent for base line safety investigations and asked to report on the next OPD date, when the results are expected to be ready. Pulse rate and supine blood pressure will be measured. The laboratory values of hematology, biochemistry with serum and urine, platelet aggregation, ECG, 2-D-Echocardiography investigated for baseline parameters in subjects.

Day 1: start of therapy:

Patients receive combination polypill (low dose) daily drug regimen for 12 weeks.

Week 1-4: once –a-week visit:

All patients who develop Dry irritating cough in the 1st 4 weeks of combination pill therapy shall be withdrawn from the study. Supine blood pressure will be measure by auscultatory method on the day of follow-up in all patients and change if any observed.

Week 4:

Subjects will be questioned for adverse events and the laboratory values of serum biochemistry, ECG, 2-D-Echocardiography investigated for the efficacy, safety and tolerability. Pulse rate and supine blood pressure will be measured. If the blood pressure is reduced with Low dose, continue with low dose. If the blood pressure is not reduced with low dose increased to medium dose.

Week 6 and 8, 12:

Subjects will be questioned for adverse events and the laboratory values of serum biochemistry, ECG, 2-D-Echocardiography investigated for the efficacy, safety and tolerability. Pulse rate and supine blood pressure will be measured in all the three visits.

The patients will receive the tablets in Visit-I, Visit-II, and Visit-III for each 4 weeks respectively. The patients are advised to report in the next visit schedule dates. At each of the visit schedule dates, patients are advised to fast for 12hrs and then the patient's blood and urine samples will be screened.

The patients will enquire about any adverse reactions or any inconvenience while under the study in every visit.

Efficacy variables:

In order to determine the efficacy of the drug combination the principle parameters are observed along with other parameters.

The parameters with their normal values includes,

Blood Pressure	120/80 mm of Hg,
LDL-cholesterol	<100 mg/dl,
Total triglycerides	< 200 mg/dl,
Heart Rate	60-70 beats/min.

Safety Variables:

The other parameters with their normal values includes,

SGOT and **SGPT** levels 0-65 mcg/L,

Serum creatinine levels 21-232 mcg/L

Serum electrolytes level

Na^+ levels 135 – 145 mmol /L

K^+ levels 3.5 - 5.1 mmol /L

Cl^- levels 95 – 106 mmol /L

Data analysis:

The major parameters to assess the efficacy of the drug combinations are blood pressure i.e., systolic and diastolic blood pressure and LDL-cholesterol, and Total Triglycerides levels in 4 visits were evaluated by using ANOVA. The comparative significance is tested and should be less than 0.05.

Adherence to Study Medication:

Study visits are conducted every four weeks and as a consequence, sufficient medication is included in the container to last for this interval. However as a crosscheck of the subject's adherence to drug therapy, each container has 28 tablets placed in it for each study visit and the subjects are not informed that the containers have additional tablets. At each study visit the subject is required to return the container. Two separate tablet counts are then conducted one by the study by the coordinator. This enables a check on adherence to therapy by calculating the difference between 28 and the days of therapy and comparing this with number of tablets left in the container.

DRUG PROFILE

Simvastatin[67]:

Simvastatin is a lactone Prodrug which is metabolized after oral ingestion to the Dihydroxy open acid form. Which inhibits 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) Reductase? An enzyme that catalyzes than early rate limiting step in the biosynthesis of cholesterol.

Clinical Pharmacology:

Simvastatin is ɣ-lactone obtained by chemical modification of Lovastatin. Hydrolysis of the lactone by esterase results in the Dihydroxy open acid originally designed by the manufacturer as L-654.969. Now known as Simvastatin Acid or S V A .Which is the active form of the compound. This active metabolite is a competitive inhibitor of HMG-CoA reductase. A key rate-limiting enzyme in the cholesterol biosynthetic pathway. The enzyme HMG- CoA reductase catalyzes the Conversion of HMG-CoA to Mevalonate.

The main mechanism of reduction of Low Density Lipoprotein (LDL) Cholesterol is that following inhibition of HMG CoA reductase activity. The LDL receptor density on the liver cell is increased (up regulation) and this leads to increased removal of LDL cholesterol from the plasma and increased catabolism of LDL Cholesterol. In addition there is a reduction in the very low density lipoprotein (VLDL) cholesterol and reduced formation of LDL from VLDL. The precursor HMG-CoA is readily metabolized back to acetyl CoA.

Pharmacokinetic properties:

Simvastatin is orally administered Prodrug, after oral administration, Simvastatin is well absorbed (≈60 to 80%) but undergoes extensive first pass metabolism. In the Liver, Simvastatin is rapidly hydrolysed from the inactive lactone form the corresponding to the active β-hydroxyacid metabolite and other less important metabolites.

Simvastatin and its active metabolites are predominantly concentrated in the liver, which is the main target site of the drug. Circulating Simvastatin and its active β-hydroxyacid metabolite are about 95% bound to plasma proteins. The elimination half-life of the major active metabolite is 1.9 hours and total body clearance is 31.8L/h. approximately 60%of the administered is recovered from the feces, 30% is recovered in the urine, almost entirely as inactive metabolites. The pharmacokinetic profile of Simvastatin is not affected when the drug is administered immediately before a low–fat meal.

Pharmacodynamic properties:

Simvastatin is an inactive prodrug which is hydrolysed in the liver to its major active β-hydroxylated metabolite, a competitive and reversible inhibitor of HMG-CoA reductase. HMG-CoA reductase is the enzyme responsible for the conversion of HMG-CoA to Mevalonic acid, a rate limiting step in the early stages of the cholesterol biosynthetic pathway. Inhibition of hepatic cholesterol biosynthesis by HMG-CoA inhibitors give rise to increased expression of low density lipoprotein (LDL) receptors in the liver which binds LDL particles and remove from the circulation, thereby lowering serum total cholesterol levels.

Therapeutic use:

1. Primary Hypercholesterolaemia (type IIa and IIb) in patients who have not responded adequately to diet and other appropriate measures.
2. Coronary heart diseases and elevated plasma cholesterol levels.

Tolerability:

Adverse events associated with Simvastatin are mild and transient and most frequently include gastrointestinal problems – Constipation, Diarrhea, Dyspepsia, Flatulence, and Nausea. In a large cohort of more than 2400 patients with Hypercholesterolemia who participated in a controlled trail and their open extensions, Simvastatin was considered to be associated with constipation in 25%, abdominal pain in 2.5%, flatulence in 2.0%, and nausea in 1.2% and dyspepsia in 0.7% of patients. Other adverse events, which occur in approximately 1 to 3% of patients, include headache, sleep disturbances and asthenia.

Data from comparative studies indicate that the tolerability profile of Simvastatin is similar to that of other HMG-CoA reductase inhibitors and similar or, in some cases, tend to be better than that of other agents such as bile acid sequestrants or fibrates.

In particular, adverse gastrointestinal effects tend to occur much less frequently with Simvastatin then with cholestyramine.

Dosage:

Simvastatin is administered orally as a single dose in the evening. The recommended starting dosage is 5 to 10mg/day which is then titrated according to individual response at intervals of at least 4weeks to a maximum dosage of 40mg/day.

Ramipril: [68]

Ramipril is a lysine derivative of Enalaprilat, the active metabolite of Enalapril.

Mechanism of action:

ACE inhibitor Ramipril is a lysine derivative of Enalaprilat; it reduces the blood pressure by reducing peripheral vascular resistance without reflexly increasing cardiac output, rate or contractility. Ramipril block the Angiotensin converting enzyme that cleaves Angiotensin I to form the potent vasoconstrictor, Angiotensin II. This inhibitor also diminishes the rate of bradykinin inactivation. Vasodilation occurs as a result of the combined effects of lower vasoconstriction caused by diminished levels of Angiotensin II and the potent vasodilating effect of increased bradykinin, by reducing circulating Angiotensin II levels. Ramipril also decreases the secretion of aldosterone, resulting in decreased sodium and water retention.

Pharmacodynamic properties:

The major action of Ramipril is the reduction in circulating levels of Angiotensin II. This is achieved by inhibition of plasma and tissue ACE. Reductions in ACE activity in patients receiving Ramipril are related to concentrations of the drug in plasma. Maximum reduction in ACE activity occurs 6 to 8 hours after administration of a single dose of Ramipril, mediated inhibition of ACE activity persists for approximately 12 to 24 hours.

Various other Neurohormonal mediators e.g. Aldosterone, endothelin, Atrial Natriuretic Peptide (ANP) and Bradykinin are involved in the progression and symptoms of heart failure. In patients with heart failure, circulating levels of vasoconstricting peptide endothelin-I are also elevated increasing with disease severity and potentiated by Angiotensin II, as well as being a potent vasoconstrictor, endothelin-I mediates cell proliferation, thus contributing to cardiac hypertrophy. The levels of these mediators are indirectly altered by Ramipril. This is increases Bradykinin levels *in vitro*, possibly through a reduction in Bradykinin degradation, and potentiates Bradykinin induced vasodilation.

Administration of Ramipril to patients with heart failure leads to a number of improvements in cardiac function:

- Decreases Angiotensin II, Aldosterone and endothelin levels in plasma
- Increases plasma renin levels
- Increases renal blood flow
- Decreases or no significant change in glomerular filtration rate and decreases filtration fraction.
- No effect on plasma catecholamine and adrenalin levels
- Increases or no change in peak oxygen conception during exercise

Pharmacokinetic properties:

Absorption of orally administered Ramipril is unaffected by food and the bioavailability of Ramipril is 25 to 50% in volunteers. In patients with heart failure, the absolute bioavailability of Ramipril is reduced approximately 16%. In volunteers and patients with heart failure, peak plasma concentration of (C_{max}) of l Ramipril after oral administration of multiple 2.5 or 5mg doses occur within approximately 6 to 8hours. C_{max} and the area under the curve over the first 96 hours (AUC0-96h) were increased in patients with heart failure compared with volunteers.

The drug is not highly plasma protein bound and the volume of distribution is 124L but this also reduced to a small extent in patients with heart failure. Ramipril does not undergo metabolism and is excreted unchanged in the urine. Because of reduced clearance of the drug in patients with heart failure.

The drug undergo 2 elimination Phases: effective elimination phase and a longer terminal elimination phase (which represents binding of the drug to ACE), which are ≈12 and 30 hours respectively. The elimination of Ramipril is decreased in patients with impaired renal function. Ramipril can be removed by Hemodialysis.

Tolerability:

Ramipril is well tolerated by patients with heart failure, and adverse events associated with its use usually do not require discontinuation of therapy. The most common adverse event was dizziness, occurring in 12% of Ramipril recipients. In addition, asthenia, angina pectoris, nausea, dysponea, cough and pruritus occurred in Ramipril treated patients but with a similar or lesser incidence then in those treated with placebo. In a longer term study of Ramipril in 620 patients the most frequent adverse event were Diziness (14%), Dysponea (7.8%), Chest pain (7.5%), Asthenia (7.0%), Cough (6.0%), Diarrohoea (6.2%), Hypotension (5.4%) and Nausea (5.2%).

Dosage:

A patient with heart failure, the recommended starting dose is 5mg in the US or 2.5mg in UK. The dose should be administered once daily and increased to the highest dose tolerated by the patient up to a maximum of 20 mg.

Aspirin: [69]

Most Heart attacks develop when a cholesterol-laden plaque in a coronary artery ruptures. Relatively small plaques, which produce only partial blockages, are the ones most likely to rupture. When they do, they attract platelets to their surface. Platelets are the tiny blood cells that trigger blood clotting. A clot, or thrombus, builds up on the ruptured plaque. As the clot grows, it blocks the artery. If the blockage is complete, it deprives a portion of the heart muscle of oxygen. As a result, muscle cells die-and it's a heart attack.

Aspirin helps by inhibiting platelets. Only a tiny amount is needed to inhibit all the platelets in the bloodstream; in fact, small amounts are better than high doses. But since the clot grows minute by minute, time is of the essence.

Pharmacodynamics:

Aspirin affects platelet aggregation by irreversibly inhibiting Prostaglandin Cyclooxygenase. This effect lasts for the life of the, platelet and prevents the formation of the platelet aggregating factor thromboxane A2.

Pharmacokinetics:

Aspirin is well and completely absorbed from the gastrointestinal (GI) tract and is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid seen within 1-2 hours of dosing. The rate of absorption is dependent upon the dosage form, the presence or absence of food, gastric pH, and other physiologic factors. Salicylic acid is widely distributed to all tissues and fluids in the body including the Central Nervous System (CNS), breast milk and fetal tissues, with highest concentrations seen in plasma, liver, renal cortex, heart and lungs. The protein binding of salisylate is non-linear at low concentrations (<100mcg/ml), approximately 90% is bound to albumin while at higher concentrations (>400mcg/ml), only about 75% is bound.

Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucouronide, and a number of minor metabolites. The half life of salicylic acid is approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentration due to limited ability of the liver to form salicyluric acid and phenolic glucuronide. Following toxic doses (10-20gm), the plasma half-life may be increased to over 20 hours. The elimination of salicylic acid follows zero order pharmacokinetics. Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5% > 80%.

Hydrochlorothiazide:

Clinical Pharmacology: [70]

Hydrochlorothiazide is a Thiazide diuretic. The Thiazides are moderately potent diuretics which act at the proximal end of the distal tubule causing a decrease in reabsorption of electrolytes and an increase in excretion of sodium and chloride ions with accompanying water loss.

The hypotensive effect is possibly due to a decrease in peripheral resistance. They are generally not effective in adults with a creatinine clearance of < 30ml/min.

The proposed mechanism of anti- hypertensive action is:[71]

1. Initially the diuresis reduces plasma and extracellular fluid volume about 15% this reduces cardiac output.
2. Subsequently compensatory mechanisms operate to almost regain NA^+ balance and plasma volume; cardiac output is restored, but the fall in BP is maintained a slowly developing reduction in total peripherial resistance.
3. The reduction in total peripherial resistance is most probably an indirect consequence of a small (5%) persisting NA^+ and volume deficit. Decrease in intracellular NA^+ concentration in the vascular smooth muscle may decrease stiffness of vessel wall, increase their compliance and dampen responsiveness to constrictor stimuli (NA, AII). Similar effects are produced by salt restriction; anti-hypertensive action of diuretics is lost when salt intake is high. A mild slowly developing vasodilator action of thiazides has been produced, but does not appear to be real. The fall in BP develops gradually over 2-4 weeks.

Pharmacokinetics: [72]

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract with a bioavailability of 65 – 70 % (adults), a half life is 5 to 15 hours (adults) and is predominantly bound to red blood cells. Elimination half life is dependent on glomerular filtration rate (creatinine clearance) and is longer than for chlorothiazide. It is excreted mainly unchanged in the urine.

Adverse Effects:

1. Hypokalaemia, hypochloraemic alkalosis, hypomagnesaemia, hypocalcaemia, hypophosphotaemia, hyponatraemia, hyperglycaemia, hyperuricaemia.
2. Small increase in excretion of bicarbonate due to decrease in carbonic-anhydrase activity.
3. Zinc deficiency.
4. Possibly kernicterus in very jaundiced babies.
5. Plasma albumin binding sites.

Dosage :

Hydrochlorothiazide comes as a tablet and liquid to take by mouth. It usually is taken once or twice a day. If you are to take it once a day, take it in the morning; if you are to take it twice a day, take it in the morning and in the late afternoon to avoid going to the bathroom during the night. Take this medication with a meal or snack. Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take hydrochlorothiazide exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor.

Hydrochlorothiazide controls high blood pressure but does not cure it. Continue to take hydrochlorothiazide even if you feel well. Do not stop taking hydrochlorothiazide without talking to your doctor.

Atenolol:

Atenolol is classified as a β_1-selective (or 'cardioselective') drug, one that exerts greater blocking activity on myocardial β_1-receptors than on β_2 receptors in the lung. The β_2 receptors are responsible for keeping the bronchial system open. If these receptors are blocked, bronchospasm with serious lack of oxygen in the body can result. However, due to its cardioselective properties, the risk of bronchospastic reactions if using atenolol is reduced compared to nonselective drugs as propranolol. Nonetheless, this reaction may also be encountered with atenolol at high doses. Although traditionally β-blockers have been contraindicated when a person carries a diagnosis of asthma, recent studies have revealed that at moderate doses selective β-blockers such as Atenolol are well tolerated.

Therapeutic use and Dosage :

Atenolol may be indicated for the following conditions at specific recommended doses. The prescription may vary and should be followed.

High blood pressure

Depending on the patient's individual response, 25 to 100 milligrams may be given daily as a single dose. It may take 1 to 2 weeks to observe full effect.

Chest pains

In single or divided doses, 50 to 100 milligram tablets may be given; this must not exceed 200 milligrams a day.

Prevention of migraine

To prevent migraine headaches, 50 to 100 milligrams may be given daily.

Emergency treatment of erratic heart beats

Once diagnosed, 2.5 milligrams may be injected intravenously at 1 milligram per minute. It may be repeated every 5 minutes if needed but must not exceed 10 milligrams. Other doctors may opt to infuse 150 micrograms of the drug for every kilo of body weight in 20 minutes. The injection or the infusion may be repeated every 12 hours as needed. Once the heart retains its rhythm, oral dose is given at 50 to 100 milligrams per day.

Heart attack

The drug may be given intravenously within 12 hours after chest pain starts. Initial dose of 5 to 10 milligrams is slowly injected at a rate of 1 milligram per minute. This can be followed by an oral dose of 50 milligrams after 15 minutes. Other physicians may opt to repeat the IV dose of 50 milligrams, 10 minutes after the last injection and then give 50 mg tablets after 12 hours. Either way, the maintenance dose will be 50 milligrams every 12 hours or 100 milligrams for 6 to 9 days after the heart attack.

RESULTS

The total numbers of patients enrolled were 30 as per the inclusion criteria of the study. All the patients were found to be complaint as per the study protocol except for three subjects, they were withdrawn from the study (patient no.5 and 23) due to his absence from visits 2, 3, 4 and one patient (patient no 10) was withdrawn from the study due to the adverse event. The total number of patients successfully completed the study were 27 as per the inclusion and exclusion criteria.

The total 27 patients were divided in to 2 groups Moderate (Systolic BP 139-159) and Severe (Systolic Bp >159) hypertensive patients according to their blood pressure levels. Out of 30 patients 23 patients are under Moderate Hypertensive and 4 No of patients under severe hypertensive patients.

Visit1 Moderate and Severe hypertensive patient's systolic and diastolic, LDL-C, Triglycerides, Total Cholesterol and HDL levels are compared with mean of visit 2, 3, 4. These comparisons are represented in the figures.

Table – 1: Moderate Systolic Hypertensive Patients Data

Moderate Systolic Hypertensive Patients Data (mm of Hg)						
S.NO	**Patient no**	**visit1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	1	150	140	140	140	140
2	4	150	140	140	130	136.6
3	7	150	140	130	140	136.6
4	8	140	130	130	120	126.6
5	9	150	140	140	140	140
6	10	150	140	140	140	140
7	11	140	120	120	120	120
8	12	140	120	130	130	126.6
9	14	140	120	120	120	120
10	15	150	140	140	130	136.6
11	16	150	160	150	120	143.3
12	17	140	130	130	130	130
13	18	150	140	160	140	146.6
14	19	150	140	130	150	140
15	20	140	150	150	130	143.3
16	22	140	130	140	150	140
17	23	140	130	130	130	130
18	24	140	140	130	130	133.3
19	25	140	140	120	130	130
20	26	140	140	140	140	140
21	27	150	140	130	140	136.6
22	28	140	140	140	130	136.6
23	29	150	150	150	130	143.3

Figure 1: Moderate Systolic Hypertensive Patients Data

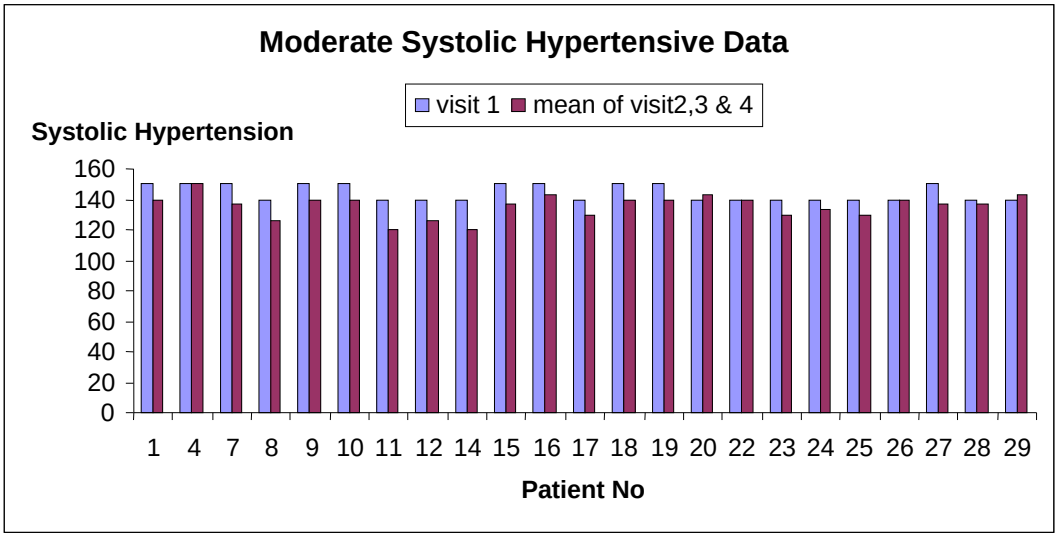


Table – 2: Moderate Diastolic Hypertensive Patients Data

Moderate Diastolic Hypertensive Patients Data (mm of Hg)						
SE.NO	**Patient no**	**Visit1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	1	100	90	80	80	83.3
2	4	100	100	90	100	96.6
3	7	100	100	80	90	90
4	8	90	80	80	80	80
5	9	90	90	90	80	86.6
6	10	90	90	90	90	90
7	11	90	80	80	90	83.3
8	12	100	80	80	80	80
9	14	100	80	80	80	80
10	15	100	100	90	90	93.3
11	16	100	90	90	70	83.3
12	17	100	80	90	80	86.6
13	18	100	100	100	100	100
14	19	100	90	90	90	90
15	20	90	90	90	100	93.3
16	22	100	90	90	90	90
17	23	90	90	80	80	83.3
18	24	100	90	90	90	90
19	25	100	90	80	90	86.6
20	26	100	100	100	100	100
21	27	90	80	90	80	86.6
22	28	100	100	90	90	93.3
23	29	100	90	90	80	86.6

Figure – 2: Moderate Diastolic Hypertensive Patients Data

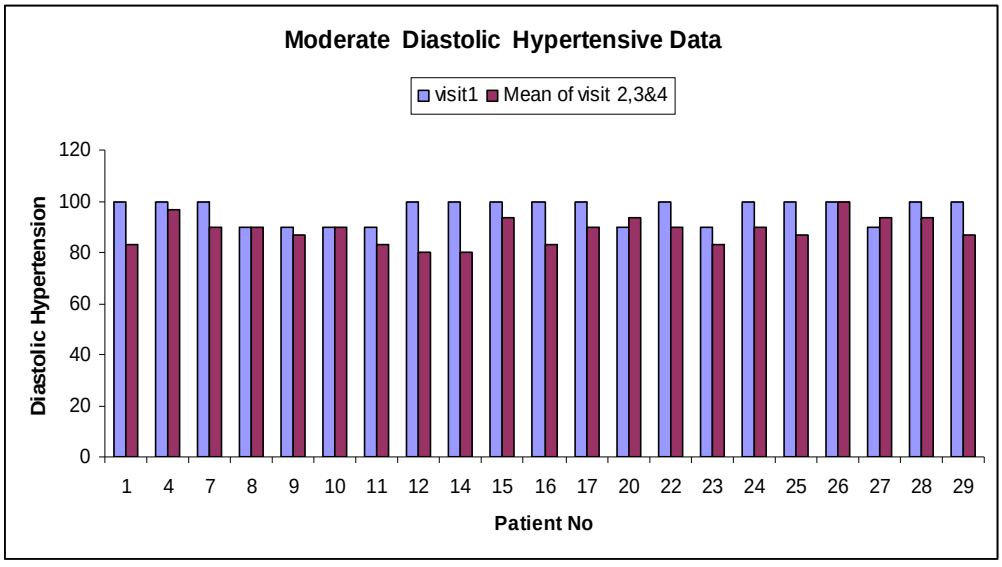


Table – 3: Moderate Hypertensive Patients LDL-C Levels

Moderate Hypertensive Patients LDL-C Levels						
S.NO	**Patient no**	**visit 1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	1	136	98	82	100	93.3
2	4	161	140	130	104	124.6
3	7	133	84	87	96	89
4	8	84	84	101	94	83
5	9	160	101	124	76	100.3
6	10	138	127	53	136	105.3
7	11	139	121	160	121	107.3
8	12	133	105	117	116	112.6
9	14	162	73	66	80	73
10	15	173	57	120	99	92
11	16	186	147	108	125	126.6
12	17	144	120	114	106	113.3
13	18	156	112	104	112	109.3
14	19	141	112	104	112	109.3
15	20	193	84	79	105	89.3
16	22	189	107	122	120	116.3
17	23	186	106	129	132	122.3
18	24	143	65	128	109	100.6
19	25	130	72	162	85	106.3
20	26	148	121	46	78	81.6
21	27	152	67	134	98	99.6
22	28	130	88	140	110	112.6
23	29	147	101	113	88	100.6

Figure – 3: Moderate Hypertensive Patients LDL-C Levels

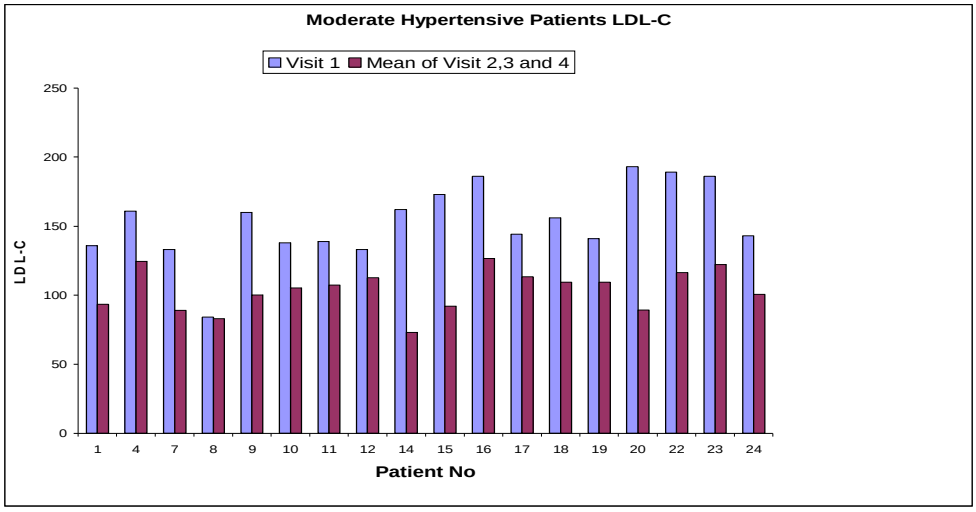


Table – 4: Moderate Hypertensive Patients Triglyceride Levels

Moderate Hypertensive Patients Triglyceride Levels						
S.NO	**Patient no**	**visit 1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	1	256	187	220	172	193
2	4	243	173	173	158	168
3	7	208	180	185	167	177.3
4	8	247	220	225	169	204.6
5	9	230	198	180	172	183.3
6	10	225	205	153	143	167
7	11	182	164	156	123	147.6
8	12	142	124	128	118	123.3
9	14	184	162	62	68	97.3
10	15	153	145	138	130	137.6
11	16	317	224	240	243	235.6
12	17	206	185	236	101	174
13	18	167	96	158	133	129
14	19	111	90	94	89	91
15	20	126	105	121	88	104.6
16	22	189	134	140	155	143
17	23	299	109	311	144	188
18	24	152	109	115	116	113.3
19	25	89	80	97	54	77
20	26	140	80	137	133	116.6
21	27	354	132	228	142	167.3
22	28	393	231	217	241	229.6
23	29	199	197	156	121	158

Figure – 4: Moderate Hypertensive Patients Triglyceride Levels

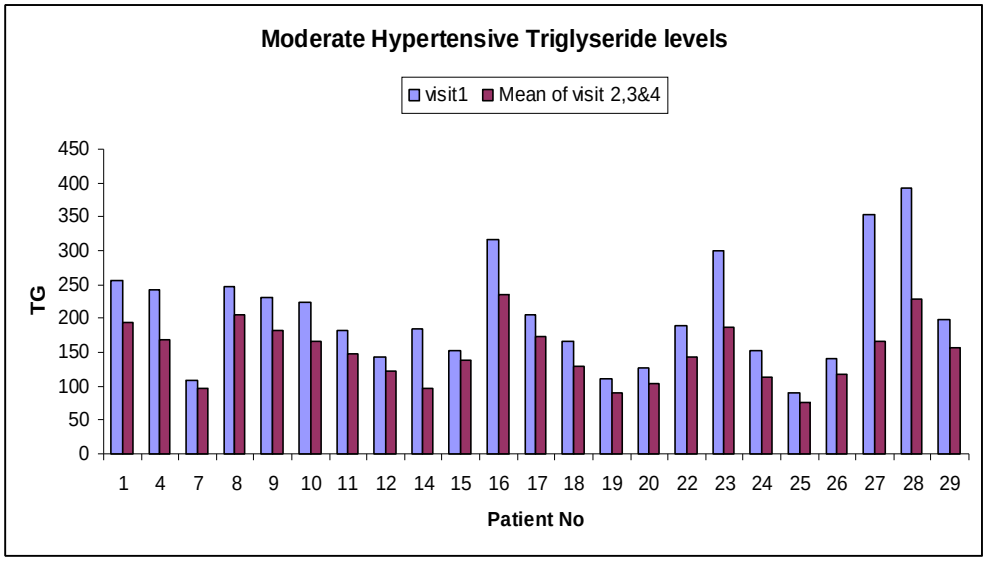


Table – 5: Moderate Hypertensive Patients Total Cholesterol levels

Moderate Hypertensive Patients Total Cholesterol levels						
S.NO	**Patient no**	**visit 1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	1	213	154	154	172	160
2	4	216	192	187	141	173.3
3	7	195	141	132	148	140.3
4	8	135	135	145	122	134
5	9	230	152	211	172	178.3
6	10	193	171	122	210	167.6
7	11	216	196	235	198	209.6
8	12	190	161	146	167	158
9	14	226	137	112	148	132.3
10	15	227	238	176	181	198.3
11	16	253	209	183	205	199
12	17	177	180	177	160	172.3
13	18	231	183	141	169	164.3
14	19	218	179	182	209	190
15	20	253	138	133	163	144.6
16	22	262	165	195	188	182.6
17	23	255	169	216	196	193.6
18	24	200	118	184	163	155
19	25	186	118	256	142	172
20	26	222	182	146	148	158.6
21	27	258	167	185	148	166.6
22	28	225	207	177	149	177.6
23	29	224	172	177	156	168.3

Figure – 5: Moderate Hypertensive Patients Total Cholesterol levels

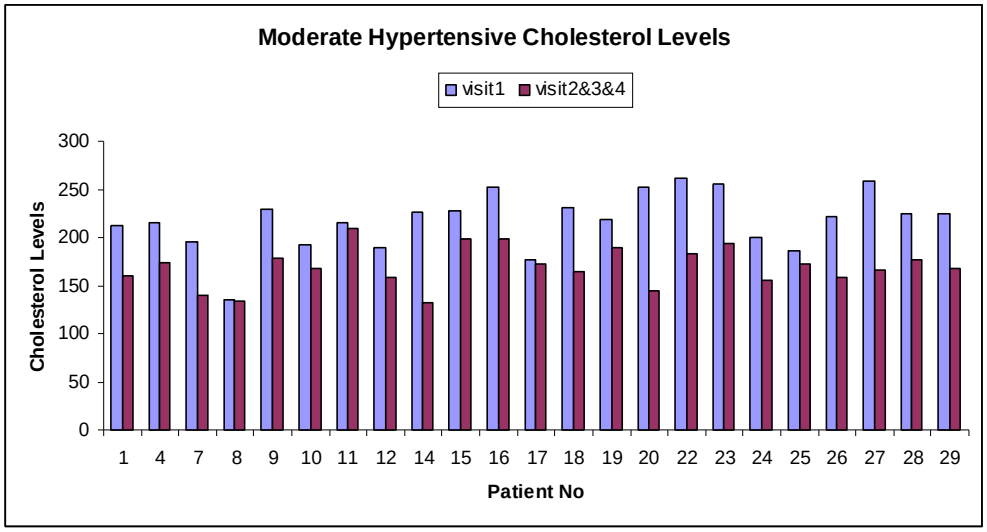


Table – 6: Moderate Hypertensive Patients HDL levels

Moderate Hypertensive HDL Levels						
S.NO	**Patient No**	**Visit 1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	1	33	36	48	56	46.6
2	4	38	48	52	63	54.3
3	7	40	38	42	56	45.3
4	8	28	28	26	31	28.3
5	9	49	42	65	67	58
6	10	34	43	57	67	55.6
7	11	59	60	67	73	66.6
8	12	31	45	42	56	51
9	14	41	40	42	55	45.6
10	15	33	27	43	56	42
11	16	28	40	45	44	43
12	17	36	40	40	58	46
13	18	55	59	56	62	59
14	19	61	54	74	68	65.3
15	20	42	55	62	64	60.3
16	22	46	38	48	62	49.3
17	23	41	43	42	57	47.3
18	24	35	36	37	42	38.3
19	25	46	43	61	48	50.6
20	26	50	53	56	62	57
21	27	43	46	53	57	52
22	28	29	32	31	31	31.3
23	29	54	53	50	51	51.3

Figure – 6: Moderate Hypertensive Patients HDL levels

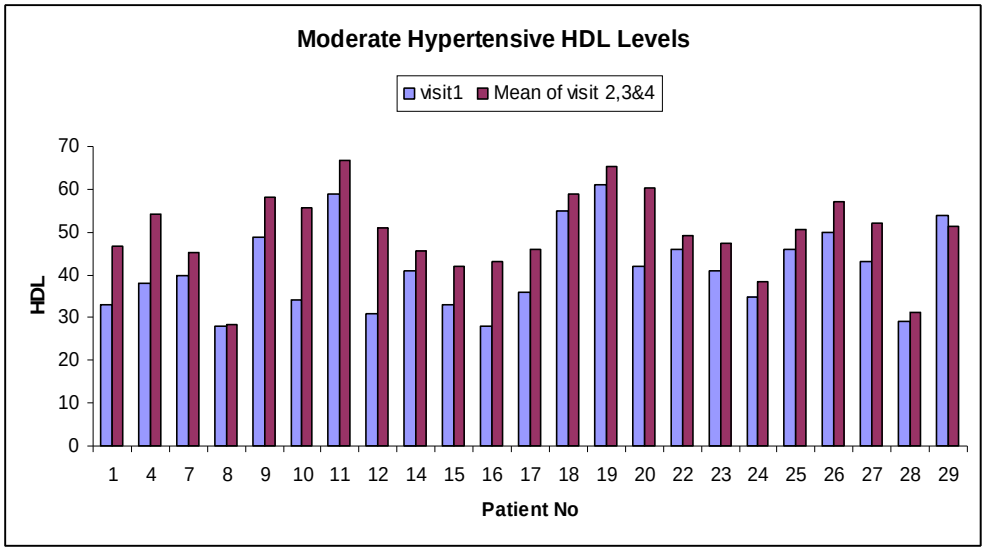


Table – 7: Severe Systolic Hypertensive Patients Data

Severe Systolic Hypertensive Patients Data						
SE.NO	**Patient no**	**Visit1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	2	160	150	130	130	136.6
2	5	160	140	120	130	130
3	6	160	150	130	130	136.6
4	13	160	130	160	130	140

Figure – 7: Severe Systolic Hypertensive Patients Data

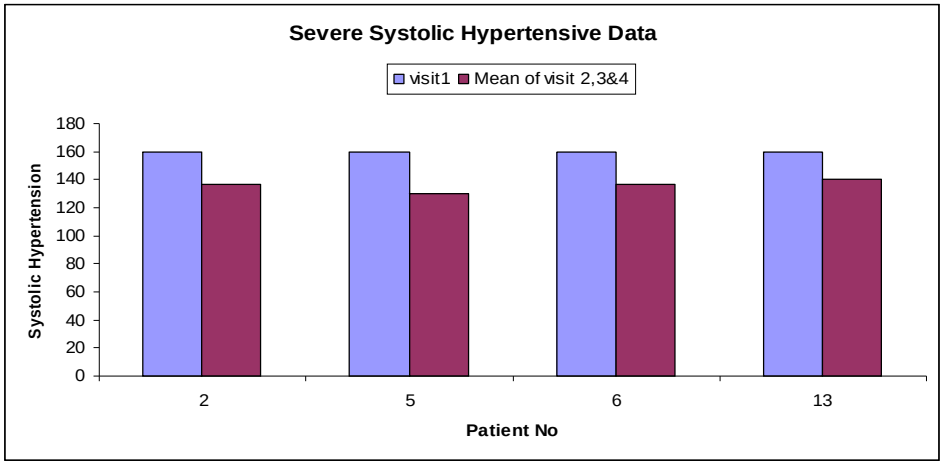


Table – 8: Severe Diastolic Hypertensive Patients Data

Severe Diastolic Hypertensive Patients Data						
SE.NO	**Patient no**	**Visit1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	2	110	100	90	85	91.6
2	5	100	80	80	90	83.3
3	6	100	90	90	90	90
4	13	110	90	82	76	82.6

Figure – 8: Severe Diastolic Hypertensive Patients Data

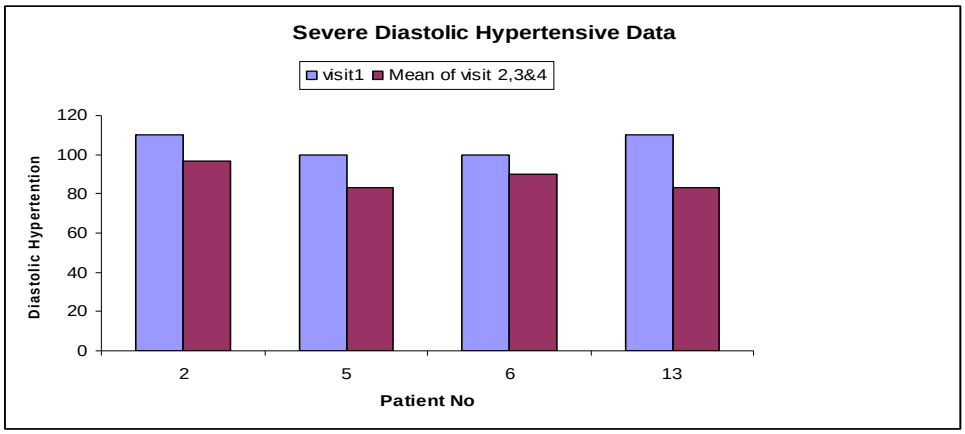


Table – 9: Severe Hypertensive Patients LDL-C Levels

Severe Hypertensive Patients LDL-C Levels						
SE.NO	Patient No	Visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	2	213	178	206	152	181
2	5	236	184	198	178	186.6
3	6	209	172	153	169	164.6
4	13	228	232	197	156	195

Figure – 9: Severe Hypertensive Patients LDL-C Levels

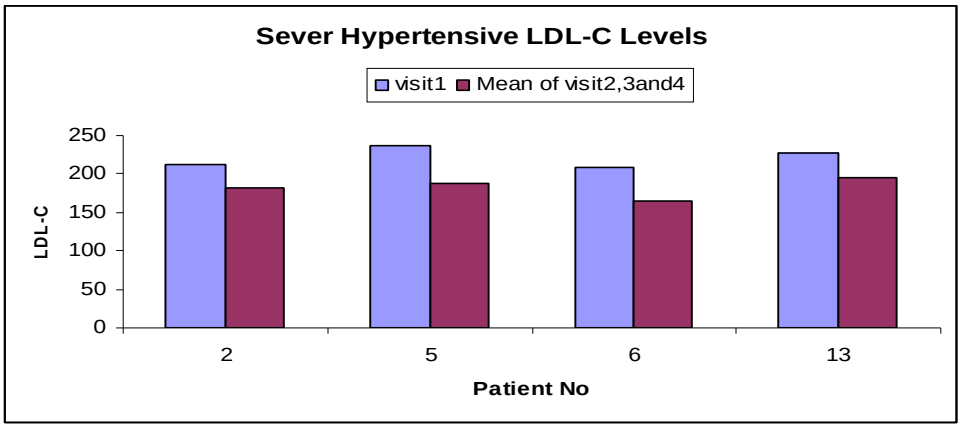


Table – 10: Severe Hypertensive Patients Triglyceride Levels

Severe Hypertensive Patients Triglyceride Levels						
SE.NO	Patient no	Visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	2	154	67	134	98	99.6
2	5	166	109	125	127	120.3
3	6	147	95	89	75	86.3
4	13	157	98	81	94	91

Figure – 10: Severe Hypertensive Patients Triglyceride Levels

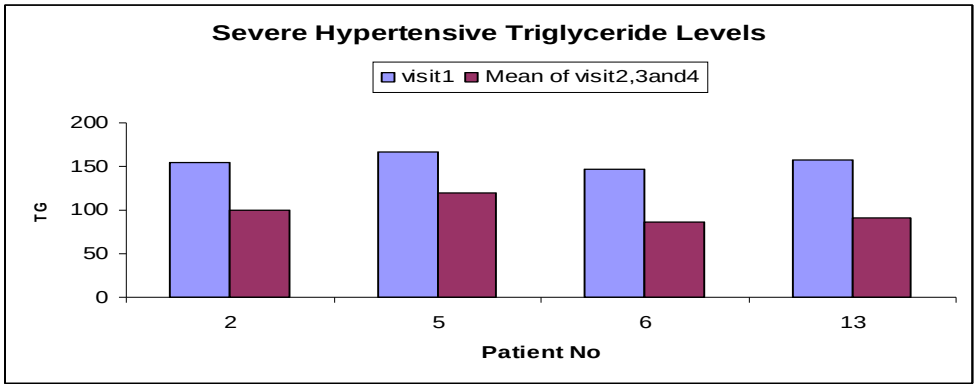


Table – 11: Severe Hypertensive Patients Total Cholesterol Levels

Severe Hypertensive Patients Total Cholesterol Levels						
SE.NO	**Patient no**	**Visit1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	2	223	120	145	147	137.3
2	5	238	171	185	198	184.6
3	6	202	143	136	128	135.6
4	13	204	149	123	145	139

Figure – 11: Severe Hypertensive Patients Total Cholesterol Levels

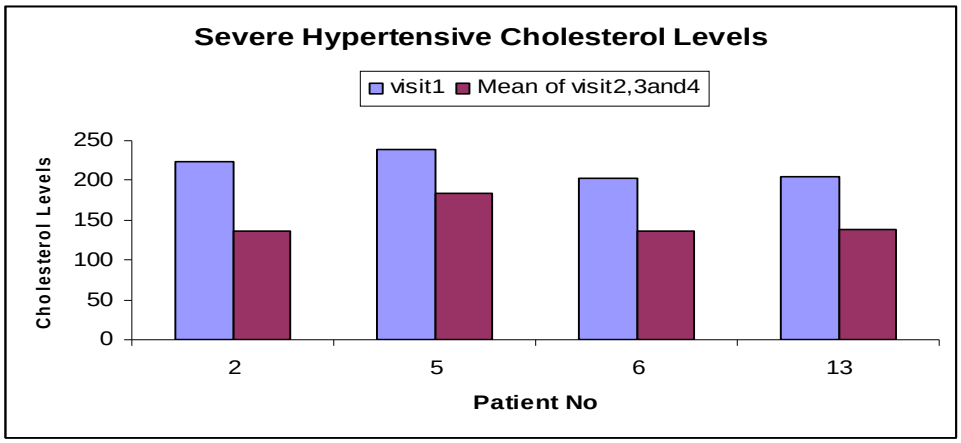


Table – 12: Severe Hypertensive Patients HDL levels

Severe Hypertensive Patients HDL levels						
SE.NO	**Patient no**	**Visit1**	**visit2**	**visit3**	**visit4**	**Mean of visit 2,3&4**
1	2	43	44	55	52	47
2	5	35	46	45	49	46.6
3	6	36	53	62	67	60.6
4	13	28	32	37	42	37

Figure – 12: Severe Hypertensive Patients HDL levels

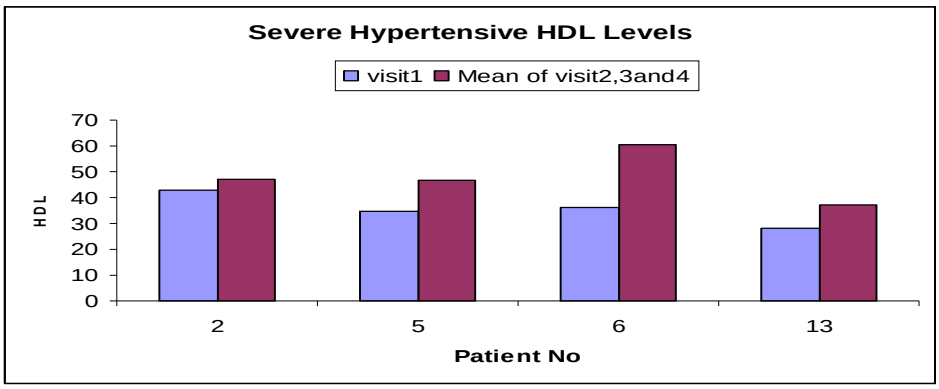


Table – 13: Efficacy of Combination Pill on Hypertension

	Systolic Hypertension		Diastolic Hypertension	
Moderate Hypertension (n = 23)	**Visit-1**	**Mean of Visit 2,3,and 4**	**Visit-1**	**Mean of Visit 2,3,and 4**
	144.78 ± 1.065	137.08 ±2.172**	96.96 ±0.981	88.67 ± 1.235***
Severe Hypertension (n=4)	160.0 ±0.00	135.8 ±2.09***	105.0 ± 2.88	86.87 ± 2.29**

n values are given as mean ±SEM

, * Values are statistically significant compared to Visit 1(Base line) at P<0.01, P<0.001 respectively

Table – 14: Efficacy of Combination Pill on Hyperlipidemia

	LDL-C		Triglycerides		Total Cholesterol		HDL	
	Visit-1	**Mean of Visit 2,3and4**	**Visit-1**	**Mean of Visit 2,3and4**	**Visit-1**	**Mean of Visit 2,3and4**	**Visit-1**	**Mean of Visit 2,3and4**
Moderate Hypertensive (n=23)	150.60±5.119	102.96±2.936***	209.21±16.047	153.30±8.95**	217.60±6.25	169.4±4.30***	41.39±2.04	49.73±1.99**
Severe Hypertensive (n=4)	221.5±6.33	181.8±6.414**	156.0±3.93	99.3±7.52***	216.75±8.51	149.12±11.8**	35.50±3.06	57.9±3.64**

n values are given as mean ±SEM

, * Values are statistically significant compared to Visit 1(Base line) at P<0.01, P<0.001 respectively

DISCUSSION

The efficacy of combination pill on Moderate Systolic Hypertensive patients was shown that P<0.05 (P=0.003). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the Systolic Blood Pressure higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Moderate Diastolic Hypertensive patients was shown that P<0.05 (P=0.001). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the Diastolic Blood Pressure higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Moderate Hypertensive patients Total Cholesterol Levels in patients was shown that P<0.05 (P=0.001). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the Cholesterol higher level and doesn't show any side effects during the 4 visits.

The efficacy of combination pill on Moderate Hypertensive patients LDL-C Levels in patients was shown that P<0.05 (P=0.001). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the LDL-C higher level and doesn't show any side effects during the 4 visits.

The efficacy of combination pill on Moderate Hypertensive patients Triglyceride Levels in patients was shown that P<0.05 (P=0.004). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the Triglyceride Levels higher level and doesn't show any side effects during the 4 visits.

The efficacy of combination pill on Moderate Hypertensive patients HDL Levels in patients was shown that P<0.05 (P=0.005). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has increased the HDL Levels higher level and doesn't show any side effects during the 4 visits.

The efficacy of combination pill on Severe Systolic Hypertensive patients was shown that P<0.05 (P=0.001). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the Systolic Blood Pressure higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Severe Diastolic Hypertensive patients was shown that P<0.05 (P=0.003). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the Diastolic Blood Pressure higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Severe Hypertensive Cholesterol Levels in patients was shown that P<0.05 (P=0.004). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the Cholesterol higher level and doesn't show any side effects during the 4 visits.

The efficacy of combination pill on Severe Hypertensive LDL-C Levels in patients was shown that P<0.05 (P=0.005). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the LDL-C higher level and doesn't show any side effects during the 4 visits.

The efficacy of combination pill on Severe Hypertensive Triglyceride Levels in patients was shown that P<0.05 (P=0.001). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has decreased the Triglyceride Levels higher level and doesn't show any side effects during the 4 visits.

The efficacy of combination pill on Severe Hypertensive HDL Levels in patients was shown that P<0.05 (P=0.003). The combination pill was considered as effective. So the combination pill show higher efficacy the drug has increased the HDL Levels higher level and doesn't show any side effects during the 4 visits.

The safety of combination pill on Moderate and Severe Hypertensive patients laboratory investigations show there is no increase in the SGOT, SGPT, Serum Creatinine and Serum electrolytes levels so the combination pill was consider as safe. The combination pill show higher safety.

CONCLUSION

The efficacy of Ramipril and Simvastatin, Aspirin, Hydrochlorothiazide combination was assessed by mean decrease in blood pressure, LDL-C, TG and Total Cholesterol level the therapy also increased HDL levels after Visit 1(screening) by application of suitable statistical parameters ANOVA. The total numbers of patients enrolled were 30 as per the inclusion and exclusion criteria of the study.

All the patients were found to be complaint as per the study protocol except for three subjects, who was withdrawn from the study (patient No.3 and 21) due to his absence from visits 2, 3, 4 and one patient (patient No 30) was withdrawn from the study due to the adverse event (Severe Dry Cough). The total number of patients successfully completed the study were 27 as per the inclusion and exclusion criteria.

Result of the present study suggest a significant decrease in the all the efficacy parameters ($p<0.005$) concluding that the drug combination has effective in decreasing the blood pressure and LDL-C levels.

The safety parameters were assessed by concentrating on the adverse drug event during the 4 visits.

Therefore, the drug combination Rampril (5mg), Simvastatin (20mg) ,Aspirin (100mg), Atenolol (50mg) and Hydrochlorothiazide (12.5mg) was found to have maximum safety with minimum adverse events reported, which is helpful in treatment of patients with hypertension and Dyslipidemia or coronary artery diseases.

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74. Corespondence to Dr.Yusuf DBCVSRI Hamilton Canada,JAMA the journal of the American Medical Association

APPENDIX

QUESTIONAIRE:

Patient Demography:

Age:---------- **Sex**: M/ F Weight (kg):---------- Height (cm):------

Marital Status: Single □ Married □ Divorced □ Widow/Widower □

Educational status: ----------

Employment status: employed □ unemployed □

1. When was your, high BP' diagnosed?

Date (year) □ Don't know □

2. What was your blood pressure reading at diagnosis? Reading:

Don't know □

3. How long did it take you to start antihypertensive management?

Immediately □

1-3mths □ 4-6mths □ 7mths-1year □

other (specify) _____

4. How long has it been since you started antihypertensive management?

1-3mths □ 4-6mths □ 7mths-1year □

other (specify) _____

5. How many antihypertensive medicines did you start with?

1 2 3 ≥4 (specify) _____.

Don't remember □

6. Please provide details of your initial antihypertensive management. Include names of medication, dosage and how often taken.

Class of AHA Name of specific drug

A. Diuretics (DIU) □

B. Angiotensin- Converting Enzyme Inhibitors (ACEI) □

C. Calcium channel blockers (CCB) □

D. Angiotensin II receptor blockers (ARB) □

E. Beta- blockers (BB) □

F. Centrally acting agents (CAA) □

G. Vasodilators (VAS) □

H. Alpha blockers (AB) □

7. Please provide details of your current antihypertensive management. Include names of medication, dosage and how often taken.

Class of AHA Name of specific drug

Diuretics (DIU) □

Angiotensin-Converting Enzyme Inhibitors (ACEI) □

Calcium channel blockers (CCB) □

Angiotensin II receptor blockers (ARB) □

Beta- blockers (BB) □

Centrally acting agents (CAA) □

Vasodilators (VAS) □

Alpha blockers (AB) □

8. What is your BP presently? Reading

9. Has your antihypertensive management changed since initial diagnosis?

Yes No

10. How many times has your drugs been changed? Once Twice

Thrice ≥ 4

11. Why were the medications changed?

Side effects □

not reaching a goal BP □

unavailability of drugs □

Personal request □

12. Please list all other medication(s), not previously mentioned in this questionnaire, that you are taking regularly or intermittently whether for this or any other condition/illness.

Name of specific drug

13. How often do you visit the Clinic in a year?

1 2 3 ≥ 4 (specify) _____

14. What side effects do you experience since taking the antihypertensive medications?

Headache /Drowsiness/ Fatigue /Cough/ Fluid Retention/ Nausea/vomiting /Decreased sex drive Diarrhea/constipation/ Flushing/ Dizziness /Body weakness/Decreased sense of taste/ loss of appetite/ erectile dysfunction

Others (specify) ----------

15. Anti-platelet drug Prescribed: ----------

16. Hypolidemic agent Prescribed: ----------

J.K.K.NATTRAJA ETHICS COMMITTEE

J.K.K.NATTRAJA COLLEGE OF PHARMACY

P.B.No 151, Natarajapuram, NH-47 (Salem to Coimbatore),
Komarapalayam - 638 183. Namakkal District, Tamil Nadu

Ref: JKKNCP/ETHICS_PRACTICE/014S02 *Date: 06.06.2014*

To
Mr. N. Venkateswaramurthy.
Department of pharmacy practice,
J.K.K. Nattraja College of Pharmacy,
Komarapalayam – 638183,
India.

Dear Mr.N.Venkateswaramurthy,

The proposal entitled "**STUDY ON FIXED DOSE COMBINATION (POLYPILL) FOR CVD PREVENTION**" was reviewed by the ethics committee in its meeting held on 06.06.2014 and permission is granted to you carry out the study.

Thanking you,

Yours faithfully,
Dr. A. Sivakumar
Chairman of Ethics committee

PRINCIPAL
J.K.K.NATARAJA DENTAL
COLLEGE & HOSPITAL
KOMARAPALAYAM - 638183.