IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 3 Ver.12 March. (2018), PP 08-21
www.iosrjournals.org

Evaluation of Safety and Efficacy of a Fixed Olmesartan / Amlodipine Combination Therapy Compared To Single Monotherapies

Dr Ankur Sharma[1], Dr Vivek Sinha [2],Dr Richa Sharma[3]

1 *Post Graduate Student,Department of General Medicine,Saraswathi Institute of Medical Science, Hapur*
2.Associate Professor ,Department Of Biochemistry,Saraswathi Institute Of Medical Sciences ,Hapur
3.Assistant Professor,Department of General Medicine,Saraswathi Institute of Medical Science, Hapur

Abstract:
Introduction
: Cardiovascular disease is a model of chronic degenerative disease, and at present is the leading cause of death worldwide, accounting for >15 million deaths each year (1). According to 2020 WHO projections, cardiovascular diseases and their complications, will be the most important cause of morbidity and death worldwide, with high costs to health-care systems (2). These forecasts reinforce the need to develop new therapeutic and preventive strategies to reduce cardiovascular disease morbidity and mortality (3).Cardiovascular diseases (CVD) account for a large proportion of all deaths and disability worldwide. India is the second most populous country in the world and emerging burden of CVD in countries here is alarming (4). In 1990, CVD accounted for 20% of all deaths in this region. Coronary heart disease (CHD) was responsible for 60% of these and 40% attributed to stroke (5).This proportion has increased to 30% and currently almost 2 million deaths are annually caused by CVD in India (6). Escalating cardiovascular risk factors are the major risk factors associated with the increasing CVD in India (7)..
Aims & Objective:
The preesent study was undertaken to estimate the prevalence of hypertension and identify & compare some socio-demographic and lifestyle risk factors associated with hypertension in urban and rural populations of Hapur.
Materials and Methods:
It's a community based cross-sectional study in which 300 adults each were randomly selected from urban and rural populations of Hapur using modified cluster sampling method. Selected individuals were examined and interviewed using a structured, pre-tested questionnaire. Two Blood Pressure readings were recorded using mercury sphygmomanometer in the sitting position and the mean of two was considered for analysis. Data entry and analysis was done using SPSS for windows version 8.1.
Result:
Most of the study population belonged to age group of 20–29 yrs (27.5%) followed by 30–39 yrs (24.5%). 41.2% of the study population was constituted by males and the rest 58.8% by females. Majority of the study population belonged to middle class (58%) followed by upper lower class (18%). The prevalence of hypertension was 21% in the present study, which is comparable to the estimates given by World Health Organization (23%).
Conclusion:
The present study identified as risk factors for the development of hypertension – increasing age, sedentary occupation, higher socio-economic status, extra salt intake, family history of hypertension, reduced physical activity, tobacco smoking, smokeless tobacco consumption, alcohol consumption, BMI ≥ 25 and high waist-hip ratio.

Keywords: *Hypertension ,prevalence ,risk factors,population*

Date of Submission: 05-03-2018 Date of acceptance: 26-03-2018

I. Introduction

Hypertension has become an important worldwide public-health challenge because of its high prevalence and concomitant risks of coronary artery disease.[4,8] People with hypertension posses two fold higher risk of developing coronary artery disease, four times higher risk of congestive heart failure and seven times higher risk of cerebrovascular disease compared to normotensive people.[9,10] •. Recent data suggests that non-communicable diseases are already the commonest cause of death in many parts of rural India.[20,22]

This is plausible as, apart from improvements in life expectancy, the greater interconnectedness increasingly allows rural populations to adopt urban lifestyles without migration to urban areas.[22,23]

Both urban and rural areas in India have been surveyed to estimate the prevalence of hypertension and a number of reviews have highlighted escalating burden of hypertension in India (11). In the mid-1950s, Indian urban population based epidemiological studies used older World Health Organization (WHO) criteria for diagnosis (known hypertension or BP >=160 mm Hg systolic and/or 95 mm Hg diastolic) and reported hypertension prevalence of 1.2 to 4.0% (12).Since then prevalence of hypertension in Indian cities has been steadily increasing from 3.0-4.5% in early 1960's to 11.0 to 15.5% in mid 1990's. Although rural populations in India generally have lower prevalence of hypertension there has been a significant increase in these populations from less than 1% in early 1960's to 5-7% in late 1990's (12).Systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg is the currently accepted diagnostic threshold for hypertension. Many prevalence studies of hypertension defined by current criteria have been performed in late 20th and early 21st century in India as reviewed earlier (13).Although hypertension is highly prevalent in India, there is low awareness, treatment and control status in Indian urban as well as rural populations. Poor control of high BP has been attributed to a variety of socioeconomic factors including women, low educational status, poverty, rural residence as well as physiological factors, e.g. obesity (13).Awareness status of hypertension has increased in the last 30 years in India but remains very low especially in rural populations (11). Hypertension awareness has increased from less than 30% in 1980's among urban populations to about 60% presently and from less than 10% in rural areas in 1980's to 35-40% presently (13). However, treatment and control status remain low at less than 30% in urban and 20% in rural areas.To achieve optimal, guideline-recommended BP targets, most hypertensive patients will require a combination of two or more BP-lowering drugs, and monotherapy would likely be sufficient only in a small proportion of patients (about 20-30%) (14). Recent international guidelines recommend initiating a two-drug combination therapy both for patients with a systolic BP more than 20 mmHg and/or a diastolic BP more than 10 mmHg above target and for patients with high cardiovascular (CV) risk (15,16).The concept of monotherapy is unlikely to achieve the same BP-lowering effect in comparison with combination therapy, as demonstrated in many studies. In a recent meta-analysis, the BP-lowering effect of combining drugs from two different classes was five times more than doubling the dose of a single drug (17,18).Therefore, it is essential and currently recommended that patients with a systolic BP more than 20 mmHg and/or a diastolic BP more than 10 mmHg above target and/or high CV risk (ie, patients with established CV disease or those with multiple CV risk factors such as metabolic syndrome, subclinical organ damage, diabetes, and renal disease) be initiated on combination therapy at diagnosis (15,16).High doses of monotherapy may lead to a better control of BP at the expense of increasing the incidence of adverse effects. When combining two drugs from different classes, lower dosages of the individual components will be enough to achieve BP target with fewer dose-related adverse effects (19). In addition, each agent in the combination can counterbalance the adverse effects of the other (20).

II. Aim And Objective

The aim of the present study is to compare the efficacy of a single Hypertensive Drug with Combination therapy

a) To achieve target BP.
b) Effect on Left Ventricular Thickness and Remodelling.
c) Effect on Lipid Profile.

This is the most prevalent Hypertension type, affecting 90–95% of Hypertension patients (23). Although no direct cause has been identified, there are many factors such as sedentary lifestyle, smoking, stress, visceral obesity, hypokalemia (24), obesity (25), of which more than 85% of cases occur in those with a body mass index greater than 25, salt (sodium) sensitivity (26), alcohol intake (27), and vitamin D deficiency that increase the risk of developing Hypertension(28,29).Risk also increases with aging (30), some inherited genetic mutations (31), and having a family history of Hypertension (32). An elevated level of renin, hormone secreted by the kidney, is another risk factor (33), as is sympathetic nervous system over activity (34). Insulin resistance also contribute to Hypertension(35,33). Some studies have implicated low birth weight as a risk factor for adult essential Hypertension(36).Secondary Hypertension by definition results from an identifiable cause. This type is important to recognize since it is treated differently to essential Hypertension, by treating the underlying cause of the elevated Hypertension(37). Some are common, well-recognized secondary causes such as renovascular Hypertension and Cushing's syndrome, which is a condition where the adrenal glands overproduce the hormone cortisol (37). Other common causes of secondary Hypertension include kidney disease, obesity, metabolic disorder, pre-eclampsia during pregnancy, the congenital defect known as coarctation of the aorta and certain prescription and illegal drugs (37-39).Adoption of healthy lifestyles by all persons is critical for the prevention of high BP and is an indispensable part of the management of those with Hypertension. Lifestyle modifications reduce BP, enhance antihypertensive drug efficacy, and decrease cardiovascular risk

Pharmacological Management:

1.**Diuretics:**Diuretics (DIU) increase urine output by the kidney. This is accomplished by altering how the kidney handles sodium. If the kidney excretes more sodium, then water excretion will also increase (49).

Loop diuretics (LDIU) inhibit the sodium-potassium-chloride co-transporter in the thick ascending limb

By acting on the thick ascending limb, which handles a significant fraction of sodium reabsorption, LDIU are very powerful DIU (51). These drugs also induce renal synthesis of prostaglandins, which contributes to their renal action including the increase in renal blood flow and redistribution of renal cortical blood flow (52). Loop diuretics are relied on for severe HPT and congestive heart failure. Example is furosemide or lasix (53).**Thiazide diuretics (TDIU)**, which are the most commonly used DIU, inhibit the sodium-chloride transporter in the distal tubule. Because this transporter normally only reabsorbs about 5% of filtered sodium, these DIU are less efficacious than LDIU in producing diuresis and natriuresis (50). Nevertheless, they are sufficiently powerful to satisfy most therapeutic needs requiring a DIU. They are considered most appropriate for mild - moderate HPT with otherwise normal heart and kidney function. Their mechanism depends on renal prostaglandin production. Examples are hydrochlorothiazide, chlorothiazide (54). Increased aldosterone stimulates sodium reabsorption and increases potassium and hydrogen ion excretion into the urine (52).There is a third class of diuretic that is referred to as potassium (K^+)-sparing DIU (examples: spironolactone, amioloride). This causes more sodium (and water) to pass into the collecting duct and be excreted in the urine. They are called K^+ -sparing DIU because they do not produce hypokalemia like the loop and thiazide DIU.The reason for this is that by inhibiting aldosterone-sensitive sodium reabsorption, less K^+ and hydrogen ion are exchanged for sodium by this transporter and therefore less K^+ and hydrogen are lost to the urine (50,52).. Because this class of DIU has relatively weak effects on overall sodiumbalance, they are often used in conjunction with thiazide or loop DIU to help prevent hypokalemia (55)

2.Alpha Blockers (AB)

Therapeutic action

These drugs block the effect of sympathetic nerves on blood vessels by binding to alpha-adrenoceptors located on the vascular smooth muscle. Most of these drugs act as competitive antagonists to the binding of norepinephrine that is released by sympathetic nerves synapsing on smooth muscle. Therefore, sometimes these drugs are referred to as sympatholytics because they antagonize sympathetic activity (54).Alpha blockers are even more effective under conditions of elevated sympathetic activity (e.g., during stress) or during pathologic increases in circulating catecholamines caused by pheochromocytoma (56).

3.Centrally-Acting Agents (CAA)

CAA blocks sympathetic activity by binding to and activating alpha2 (α2)- adrenoceptors. This reduces sympathetic outflow to the heart thereby decreasing cardiac output by decreasing heart rate and contractili. Reduced sympathetic output to the vasculature decreases sympathetic vascular tone, which causes vasodilation and reduced systemic vascular resistance, which decreases arterial pressure (57) .Centrally acting agents are used in the treatment of Hypertension.. CAA are effective in HPT patients with renal disease because they do not compromise renal function (57).

Choice of antihypertensive drugs

.Where two drugs are unable to control the BP adequately, a third agent can be added to the existing regimen (61).It has been observed that when these agents are used alone, effectiveness is limited to about 30%. Monotherapy controls BP effectively for those clients who are in stage one of HPT. Most clients in stage 2 (and stage 3, if applicable) will need a combination of two or more antihypertensive drugs. Combinations of AHA can yield an efficacy rate of not less than 60% (62).

III. Materials And Methods

Study Design

The present study is a Randomized, Prospective and Comparative study in Saraswati Institute of Medical Sciences and Hospital, Hapur (UP).

Study Area: The study was conducted in District Hapur (UP), India.

Study Period:

The study was conducted from August 2015 to June2017.

Study Setting:

The study was carried out from the patients being referred to the Department of General Medicine, Saraswati Institute of Medical Sciences and Hospital, Hapur (Uttar Pradesh).

Study Population:

A total of 120 individuals were recruited in the study. In the present series, the subjects were diagnosed with hypertension with no further immediate medical complications.

SELECTION OF CASES

Inclusion Criteria:

1. Adult patients (aged 18 years or more) reporting first time/regularly associated with SIMS hospital for management of Hypertension issue are selected.
2. Only mild to moderate grade hypertensive patients were taken
3. Patients consenting for the study

Ethical Approval:

Ethical Approval was taken from the Institutional Ethical Committee after explaining the Aim and Objectives of the Study.All patients underwent a clinical and laboratory evaluation. The demographic data were obtained from a questionnaire survey.

Study Groups:

Patients were equally randomized in three study groups: Olmesartan + Amlodipine (combination) group, olmesartan group and amlodipine group of 40 subjects each. Recommended doses were administered and patient compliance was noted. Biochemical and blood pressure analysis was performed at follow-up visits and compared at end of 4-week and 8-week period. The data were recorded by the use of a unified protocol consisting of questionnaire and clinical examination after taking verbal consent from the patients.

Specimen Collection:

Specimen Collection: Five mL of venous blood was drawn from each subject. It was dispensed into fluoride oxalate bottles for plasma glucose estimation. One EDTA vial containing 0.5 mL of it was used for estimation of glycosylated haemoglobin and the rest of the blood sample was discharged into a plain sample bottle and allowed to clot.The serum was separated from the red blood cells, divided it into three aliquots and stored them frozen at -20 degree C. Plasma glucose was determined on the same day while all other tests were done within 2 weeks of collection.Plasma glucose estimation was done by the glucose–oxidase peroxidase method, and TSH, T4 and T3 by enzyme immunoassay (EIA) kit method using commercial kits

Statistical Analysis:

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) for Windows (version 15.0). Mann–Whitney test was used for statistical comparisons. Categorical variables were compared between two or more groups using the Chi-square test. For all analyses, a two-tailed p-value of <0.05 was considered statistically significant.

IV. Observations And Result

The study was carried out among 120patients voluntarily consenting to be a part of the study. These patients were diagnosed with mild to moderate hypertension with no further severe complications and referred to the Department of General Medicine, Saraswati Institute of Medical Sciences and Hospital, Hapur (Uttar Pradesh).

Socio-demographic profile of the study participants

The age wise distribution of study participants showed that majority of them was in the age group of 31-50 years. The mean age of the study group was 46.3$\pm$12.7 years (mean$\pm$s.d.) and range=21-72 years (Table 1).

The maximum age group seen among the study subjects was 41-50 years, having 40 subjects, followed by 31-40 years, having 36 subjects, then >60 years, having 21 subjects, and then 51-60 years, having 13 subjects

Figure 1: Age wise distribution of study participants:

Table 1: Age wise distribution of study participants (n=100)

		Frequency	Percent (%)
Age group (years)	18-30	10	8.3
	31-40	36	30.0
	41-50	40	33.3
	51-60	13	10.8
	>60	21	17.5
	Total	120	100.0

The gender wise distribution of study participants showed that majority of them were males (77%) and 23% were females (Figure 2).

Figure 2: Gender distribution of study participants:

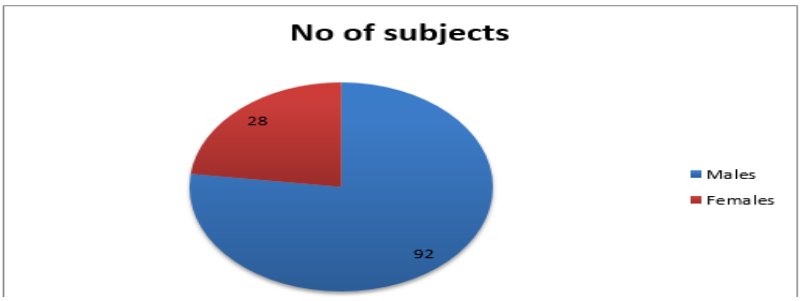
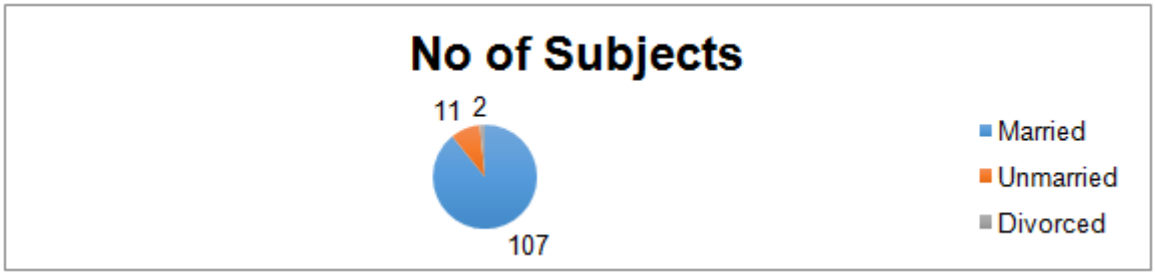


Table 2: Gender distribution of study participants

		Frequency	Percent (%)
Gender	Males	92	77
	Females	28	23
	Total	120	100

The marital status of study participants showed that majority of them were married (89%), only 9% individuals were unmarried and 2% were divorced (Figure 3).

Figure 3: Marital status distribution of study subjects
Table 3: Marital status distribution of study subjects:



		Frequency	Percent (%)
Marital status	Married	107	89
	Unmarried	11	9
	Divorced	2	2
	Total	120	100

Socio-economic status of study participants according to Modified Kuppuswamy scale 2016, showed that majority of subjects (79%) belonged to middle class, followed by 14% in lower middle class, 5% in upper middle class and 2% in upper class
(Figure 4).

Figure 4: Socio-economic status of study participants:

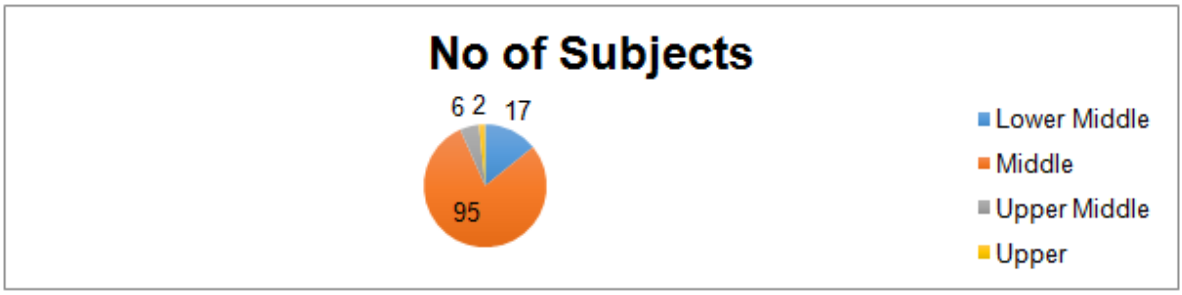


Table 4: Socio-economic status of study participants:

		Frequency	Percent (%)
Socio-economic status	Lower Middle	17	14.2
	Middle	95	79.2
	Upper Middle	6	5.0
	Upper	2	1.7
	Total	120	100.0

The religion of study participants showed that majority of them were Hindus (70%), and remaining 30% were Muslims (Figure 5).

Figure 5: Religion of study participants

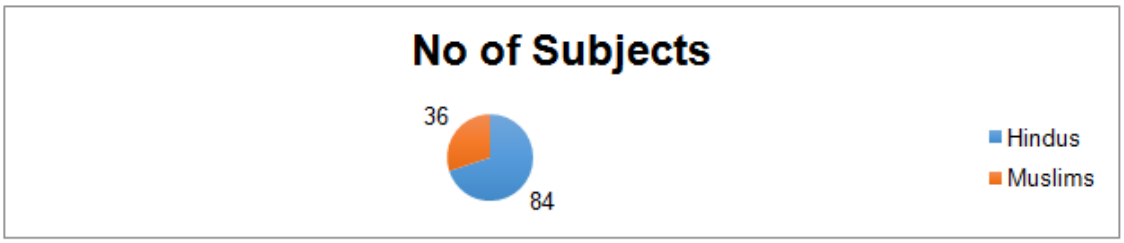


Table 5: Religion of study participants:

		Frequency	Percent (%)
Socio-economic status	Hindus	84	70.0
	Muslims	36	30.0
	Total	120	100.0

Table 6 shows the descriptive statistics of subject's vitals, such as Pulse rate, Weight in kgs and Temperature in Fahrenheit. The mean pulse rate of study participants was 78.2 with a standard deviation of 9.74 (range 64-94). The mean weight of study participants was 88.9 kg with a standard deviation of 10.2 kgs (range 75-111kgs). The mean temperature of study participants was 97.8 with as standard deviation of 0.9 (range 96-100).

Table 6: Vitals of study subjects:

		Pulse	Weight	Temperature
N		120	120	120
Mean		78.18	88.87	97.78
Median		.888	.935	.084
Mode		78.00	89.00	98.00
Std. Deviation		9.724	10.243	.921
Range		64	75	96
Minimum		94	111	100
Maximum		120	120	120
Percentiles	25	68.50	81.00	97.00
	50	78.00	89.00	98.00
	75	88.00	93.00	98.00

Table 7 and Table 8 shows the descriptive statistics of baseline levels of study parameters among all individuals, such as thyroid hormone levels (Serum T3, Serum T4, and Serum TSH levels), Kidney function tests (Blood Urea Nitrogen (BUN) and Serum Creatinine levels), Blood uric acid, Random blood sugar, Lipid profile (Total cholesterol, HDL, LDL, and triglyceride levels), Liver function tests (SGOT, SGPT, LDH and Alkaline phosphatase levels) and Serum Creatinine Kinase levels.

Table 7 shows the estimates of thyroid hormones, where Serum T3 has a mean value of 68.4, with a standard deviation of 11.0 (range 52-91), Serum T4 has a mean value of 3.3, with a standard deviation of 0.6 (range 2.2-4.2), Serum TSH has a mean value of 9.0, with a standard deviation of 1.9 (range 5.9-12.3).

Kidney function tests estimates showed that Blood urea had a mean value of 45.3, with a standard deviation of 13.5 (range 25-81), and Serum Creatinine had a mean value of 2.3, with a standard deviation of 0.6 (range 1.0-3.2). uric acid had a mean value of 5.3, with a standard deviation of 0.8 (range 4.2-6.5), random blood sugar had a mean value of 116.5, with a standard deviation of 11.5 (range 98-130) and CK had a mean value of 195.7, with a standard deviation of 23.7 (range 159-241).

T able 7: Baseline estimates of study parameters

		Thyroid hormone			**KFT**		**Uric acid**	**RBS**	**CK**
		Serum T3	**Serum T4**	**Serum TSH**	**Blood Urea**	**Serum Creat**			
N		120	120	120	120	120	120	120	120
Mean		68.38	3.305	9.033	45.33	2.283	5.341	116.54	195.74
Std. Error		1.006	.0572	.1695	1.236	.0548	.0697	1.050	2.163
Median		66.00	3.300	8.900	43.50	2.300	5.200	121.00	192.00
Std. Dev		11.015	.6263	1.8567	13.537	.6002	.7633	11.507	23.697
Minimum		52	2.2	5.9	25	1.0	4.2	98	159
Maximum		91	4.2	12.3	81	3.2	6.5	130	241
Percentiles	25	60.00	2.900	7.800	32.00	1.900	4.800	107.00	182.00
	50	66.00	3.300	8.900	43.50	2.300	5.200	121.00	192.00
	75	75.00	3.800	10.300	51.00	2.700	6.000	127.00	211.00

Lipid profile among study subjects showed that Total cholesterol had a mean value of 246.1, with a standard deviation of 39.2 (range 185-308); HDL estimates had a mean value of 41.2, with a standard deviation of 3.2 (range 37-47); LDL estimates showed a mean value of 138.7, with a standard deviation of 30.4 (range 95-195); and triglyceride had a mean level of 199.4, with a standard deviation of 28.4 (range 159-249).

Liver function tests estimates showed that SGOT had a mean value of 35.9, with a standard deviation of 6.8 (range 22.7-47.0); SGPT had a mean value of 57.7, with a standard deviation of 11.6 (range 34-73); LDH had a mean value of 242.2, with a standard deviation of 32.6 (range 185-293); and Alkaline phosphatase had a mean value of 126, with a standard deviation of 20.4 (range 95-166).

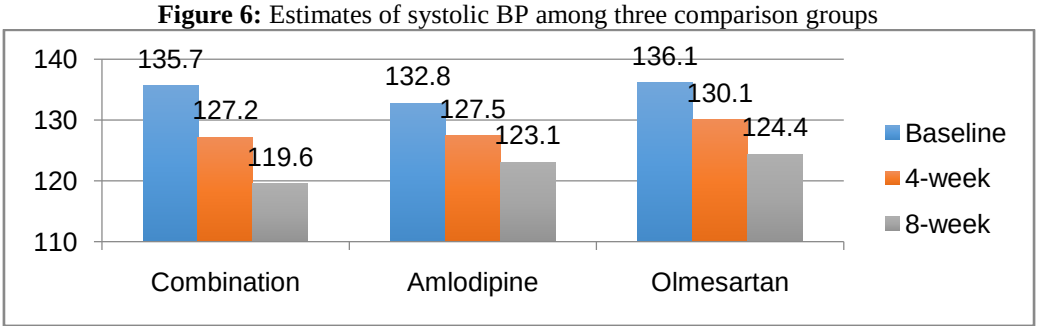
Table 8: Baseline estimates of study parameters

		Total Cholesterol	**HDL**	**LDL**	**Triglyceride**	**SGOT**	**SGPT**	**LDH**	**ALP**
N		120	120	120	120	120	120	120	119
Mean		246.08	41.19	138.69	199.38	35.918	57.74	242.31	126.00
Std. Error		3.582	.290	2.779	2.595	.6178	1.059	2.979	1.872
Median		251.00	41.00	130.00	200.00	38.300	61.00	231.00	128.00
Std. Devi		39.242	3.176	30.437	28.423	6.7677	11.605	32.629	20.426
Minimum		185	37	95	159	22.7	34	185	95
Maximum		308	47	195	249	47.0	73	293	166
Percentiles	25	208.00	39.00	108.00	171.00	29.100	50.00	217.00	106.00
	50	251.00	41.00	130.00	200.00	38.300	61.00	231.00	128.00
	75	280.00	44.00	169.50	223.00	40.100	69.00	275.00	139.00

Table 9: Estimates of systolic BP among three comparison groups

	Baseline Systolic BP		**4-week systolic BP**		**8-week systolic BP**		**p-value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Combination	135.7	10.2	127.2	8.2	119.6	9.1	0.024*
Amlodipine	132.8	9.4	127.5	8.3	123.1	10.2	0.031*
Olmesartan	136.1	10.6	130.1	6.8	124.4	8.4	0.048*
p-value	0.372		0.652		0.564		

Figure 6: Estimates of systolic BP among three comparison groups



The mean value of baseline diastolic BP in subjects receiving combination therapy was 100.7 with a standard deviation of 7.5. The mean value of 4-week diastolic BP in subjects receiving combination therapy was 92.4 with a standard deviation of 4.3. The mean value of 8-week diastolic BP in subjects receiving combination therapy was 89.6 with a standard deviation of 5.8. The mean value of baseline diastolic BP in subjects receiving amlodipine therapy was 96.4 with a standard deviation of 9.1. The mean value of 4-week diastolic BP in subjects receiving amlodipine therapy was 93.1 with a standard deviation of 6.5. The mean value of 8-week diastolic BP in subjects receiving amlodipine therapy was 92.5 with a standard deviation of 7.9.The mean value of baseline diastolic BP in subjects receiving olmesartan therapy was 102.1 with a standard deviation of 8.7. The mean value of 4-week diastolic BP in subjects receiving olmesartan therapy was 93.4 with a standard deviation of 5.7. The mean value of 8-week diastolic BP in subjects receiving olmesartan therapy was 92.8 with a standard deviation of 6.3.

Table 10: Estimates of diastolic BP among three comparison groups

	Baseline Diastolic BP		**4-week Diastolic BP**		**8-week Diastolic BP**		**p-value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Combination	100.7	7.5	92.4	4.3	89.6	5.8	0.011*
Amlodipine	96.4	9.1	93.1	6.5	92.5	7.9	0.041*
Olmesartan	102.1	8.7	93.4	5.7	92.8	6.3	0.038*
p-value	0.389		0.347		0.688		

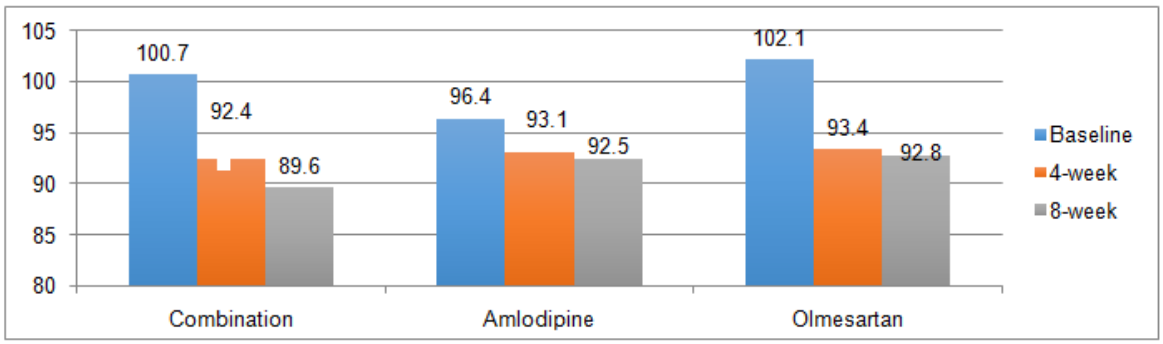


Figure 7: Estimates of diastolic BP among three comparison groups

Table 11 shows the relative Systolic and Diastolic BP change in comparison among three study groups. The difference in relative reduction among study groups was significant, with combination therapy showing the maximum decrease.

Table 11: Comparison of systolic and diastolic BP change among study groups:

	Relative change (baseline estimates with 8-week estimates)			**p-value**
	Combination	**Amlodipine**	**Olmesartan**	
Systolic BP	11.2%	9.2%	8.1%	0.003*
Diastolic BP	13.1%	9.6%	7.2%	0.017*

Estimation of any cardiovascular abnormality by Baseline Echocardiogram (ECG) showed that only 25% subjects had an abnormal ECG, and 75% patients had a normal ECG (Figure 8). At 8-week follow up, only 27% subjects had abnormal ECG and 73% subjects had a normal ECG. This difference was statistically not significant (p>0.05).

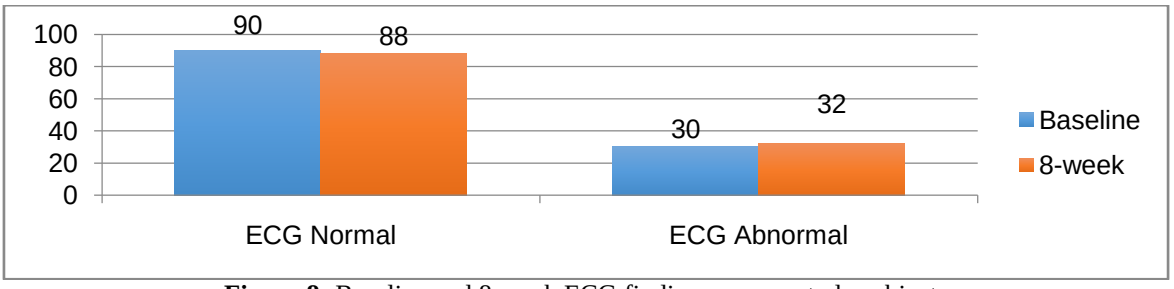


Figure 8: Baseline and 8-week ECG findings among study subjects

Table 12: ECG findings among study subjects

		Baseline		8-week		p-value
		Frequency	Percent (%)	Frequency	Percent (%)	
ECG findings	Normal	90	75	88	73	0.945 (not significant)
	Abnormal	30	25	32	27	
	Total	120	100.0	120	100.0	

Table 13, Table 14 and Table 15 shows the study parameters at baseline and 8-week follow-up in subjects receiving combination, amlodipine and olmesartan therapy. None of the study parameters except CK had a significant decline over the 8-week time period.

Table 13: Estimation of study parameters at baseline and 8-week follow-up in patients receiving combination therapy:

	Baseline		8-week		p-value
	Mean	SD	Mean	SD	
Serum T3	68.33	11.065	67.93	11.244	0.745
Serum T4	3.348	.6139	3.280	.6521	0.783
Serum TSH	9.125	1.931	9.063	1.851	0.235
Blood Urea	48.23	13.007	43.88	14.450	0.726
Serum Creatinine	2.275	.6306	2.333	.5619	0.454
RBS	116.88	11.625	116.07	11.609	0.124
Uric acid	5.340	.7811	5.330	.7884	0.345
CK	197.33	24.831	193.58	22.955	0.006*
Total cholesterol	246.92	39.556	245.90	39.977	0.564
HDL	41.13	3.345	41.25	3.061	0.678
LDL	136.33	30.821	136.70	30.051	0.789
Triglyceride	201.98	27.702	193.52	28.979	0.678
SGOT	36.103	6.8651	35.998	6.5965	0.348
SGPT	58.65	11.570	58.35	11.853	0.239
LDH	245.52	34.053	240.67	31.772	0.215
AlkPhosp	126.46	20.366	127.20	21.856	0.564

Table 14: Estimation of study parameters at baseline and 8-week follow-up in patients receiving amlodipine therapy:

	Baseline		8-week		p-value
	Mean	SD	Mean	SD	
Serum T3	67.12	10.245	66.84	10.474	0.456
Serum T4	2.138	0.2061	2.19	0.1179	0.786
Serum TSH	7.915	1.111	7.973	1.081	0.982
Blood Urea	47.02	12.187	42.79	13.68	0.989
Serum Creatinine	1.065	0.1894	1.243	0.2081	0.761
RBS	115.67	10.805	114.98	10.839	0.984
Uric acid	4.13	0.0389	4.24	0.0184	0.911
CK	196.12	24.011	192.49	22.185	0.008*
Total cholesterol	245.71	38.736	244.81	39.207	0.134
HDL	39.92	2.525	40.16	2.291	0.237
LDL	135.12	30.001	135.61	29.281	0.972
Triglyceride	200.77	26.882	192.43	28.209	0.754
SGOT	34.893	6.0451	34.908	5.8265	0.199
SGPT	57.44	10.75	57.26	11.083	0.274
LDH	244.31	33.233	239.58	31.002	0.861
AlkPhosp	125.25	19.546	126.11	21.086	0.972

Table 15: Estimation of study parameters at baseline and 8-week follow-up in patients receiving olmesartan therapy

	Baseline		**8-week**		**p-value**
	Mean	**SD**	**Mean**	**SD**	
Serum T3	68.2	10.945	67.49	11.034	0.289
Serum T4	3.218	0.4939	2.84	0.4421	0.891
Serum TSH	8.995	1.811	8.623	1.641	0.072
Blood Urea	48.1	12.887	43.44	14.24	0.812
Serum Creatinine	2.145	0.5106	1.893	0.3519	0.824
RBS	116.75	11.505	115.63	11.399	0.762
Uric acid	5.21	0.6611	4.89	0.5784	0.235
CK	197.2	24.711	193.14	22.745	0.005*
Total cholesterol	246.79	39.436	245.46	39.767	0.149
HDL	41	3.225	40.81	2.851	0.198
LDL	136.2	30.701	136.26	29.841	0.487
Triglyceride	201.85	27.582	193.08	28.769	0.454
SGOT	35.973	6.7451	35.558	6.3865	0.197
SGPT	58.52	11.45	57.91	11.643	0.971
LDH	245.39	33.933	240.23	31.562	0.198
AlkPhosp	126.33	20.246	126.76	21.646	0.662

Table 16 shows the relative change in study parameters in comparison among three study groups. The difference in relative reduction among study groups was non-significant in all the parameters, except for CK where combination therapy showed the maximum decline, which was significant.

Table 16: Comparison of study parameters among three study groups:

	Relative change (baseline estimates with 8-week estimates)			**p-value**
	Combination	**Amlodipine**	**Olmesartan**	
Serum T3	2.2%	1.2%	3.1%	0.223
Serum T4	3.1%	1.6%	4.2%	0.134
Serum TSH	4.8%	2.1%	2.5%	0.534
Blood Urea	1.5%	4.5%	3.1%	0.422
Serum Creatinine	2.6%	6.1%	2.8%	0.296
RBS	5.3%	2.3%	4.8%	0.592
Uric acid	6.1%	3.8%	3.3%	0.588
CK	15.4%	12.4%	12.1%	0.032*
Total cholesterol	4.0%	5.1%	6.3%	0.626
HDL	3.6%	3.2%	4.4%	0.756
LDL	2.1%	3.3%	3.8%	0.273
Triglyceride	1.8%	1.5%	1.8%	0.263
SGOT	2.4%	5.3%	4.3%	0.786
SGPT	5.2%	4.9%	3.5%	0.726
LDH	7.1%	2.9%	5.2%	0.652
AlkPhosp	5.8%	3.6%	5.1%	0.711

V. Discussion

The present study was envisaged to study the effectiveness of combination therapy vs monotherapy with olmesartan (OLM) and amlopdipine (AML).These findings with a combination of olmesartan and amlodipine are in line with the results both from comparable studies of other fixed-dose combinations and from other studies specifically investigating a combination with a different ARB: valsartan with amlodipine. (70,71).There were reductions in blood pressure with monotherapy of olmesartan and amlodipine that were also significant but not to the extent as seen with dual therapy of the two drugs. Similar results were obtained in study done by Zhang et al in 2017. (72) These findings have implications on management of hypertension. A series of articles have reported that olmesartan/amlodipine combination produced benefits in increasing insulin sensitivity and decreasing inflammatory markers compared to any of them, which can tremendously benefit the hypertensive patients with multiple symptoms. (73,74) .Sievers's study found that combined treatment with olmesartan and amlodipine attenuated atherosclerotic lesion progression, possibly due to anti-inflammatory mechanisms, even in advanced atherosclerosis. (70).Both the European and the American guidelines for the treatment of hypertension indicate the importance of combination therapy in achieving the blood pressure goals more rapidly. (69,76).Volpe et al demonstrated that more than 70% of patients treated actively with the combination therapy of OLM/AML 20/5 mg achieved their BP goal by Week 24. (77).There were also several studies comparing olmesartan with amlodipine for mild-to-moderate hypertension. Chrysant's study (78) revealed that though mean reductions in ambulatory and seated BP were similar between the two agents group and both were well tolerated at the recommended starting dose, more patients in the olmesartan group achieved the SBP goal of <130 mmHg and the DBP goal of <85 mmHg.This conclusion was also confirmed by

Chrysant's further study. (79). Our study revealed that effect of treatment whether dual or montherapy did not have much effect on ECG findings at the end of 8 weeks treatment. Recent outcome studies in high-risk hypertensives have shown that ARBs provide cardiovascular-renal protection beyond what can be entirely attributed to BP-lowering alone. (80).

However, the follow up period in our study was too short to document any such effect on ECG. But findings of the CAFÉ study, which showed that the improved cardiovascular protective effects of the CCB/ACE-I combination may be attributed to a greater reduction of central rather than brachial systolic blood pressure. (81).Except for the creatinine kinase, none of other variables showed any significant change with combination therapy or mono-therapy in the present study. Evidence suggests higher proportion of persistent high CK in hypertensive vs normotensive persons. (82) It has been hypothesized, in a biological plausible manner, that high creatine kinase (CK) activity could be a genetic factor responsible for primary hypertension.High CK has also been associated with failure of antihypertensive therapy. (83) In addition, a low CK level was associated with lower BP. There are few reports of ARBs affecting hepatic function. There was no significant difference in the levels of ALT and AST from baseline to six months of use of losartan in hypertensive diabetic patients. (84) Supporting these reports, there was no statistically significant difference in the serum levels of ALT and AST between baseline and the exposure period in both ARB users and CCB users in our study. In addition, those changes from baseline to during the exposure period were not significantly different between ARB and CCB users. Therefore, the influence of ARB and CCB monotherapy on hepatic function may be minimal and not of clinical concern.

VI. Conclusion

When a doctor prescribes medicines to reduce the blood pressure for the first time, he or she has two options, using only one medicine (called mono therapy) or using two medicines (called combination therapy). The potential advantage of using combination therapy is that blood pressure could fall faster, but we do not know if this is better or worse for avoiding health problems.The current study depicting the reduction in systolic and diastolic blood pressure with combination therapy showed consistent decline from baseline to end of 8 weeks treatment. The findings were significant. There were reductions in blood pressure with monotherapy of olmesartan and amlodipine that were also significant but not to the extent as seen with dual therapy of the two drugs.These findings recommend combination therapy, if indicated, as initial therapy when a reduction exceeding 20/10 mmHg is required to attain the blood pressure goals.

VII. Summary

The age wise distribution of study participants showed that majority of them was in the age group of 31-50 years. The mean age of the study group was 46.3$\pm$12.7 years (mean$\pm$s.d.) and range = 21-72 years. The gender wise distribution of study participants showed that majority of them was males (77%).

The mean pulse rate of study participants was 78.2 with a standard deviation of 9.74 (range 64-94). The mean weight of study participants was 88.9 kg with a standard deviation of 10.2 kgs (range 75-111kgs). The mean temperature of study participants was 97.8 with as standard deviation of 0.9 (range 96-100).

Serum T3 has a mean value of 68.4, with a standard deviation of 11.0 (range 52-91), Serum T4 has a mean value of 3.3, with a standard deviation of 0.6 (range 2.2-4.2), Serum TSH has a mean value of 9.0, with a standard deviation of 1.9 (range 5.9-12.3).

Kidney function tests estimates showed that Blood urea had a mean value of 45.3, with a standard deviation of 13.5 (range 25-81), and Serum Creatinine had a mean value of 2.3, with a standard deviation of 0.6 (range 1.0-3.2). uric acid had a mean value of 5.3, with a standard deviation of 0.8 (range 4.2-6.5), random blood sugar had a mean value of 116.5, with a standard deviation of 11.5 (range 98-130) and CK had a mean value of 195.7, with a standard deviation of 23.7 (range 159-241).

Lipid profile among study subjects showed that Total cholesterol had a mean value of 246.1, with a standard deviation of 39.2 (range 185-308); HDL estimates had a mean value of 41.2, with a standard deviation of 3.2 (range 37-47); LDL estimates showed a mean value of 138.7, with a standard deviation of 30.4 (range 95-195); and triglyceride had a mean level of 199.4, with a standard deviation of 28.4 (range 159-249).

Liver function tests estimates showed that SGOT had a mean value of 35.9, with a standard deviation of 6.8 (range 22.7-47.0); SGPT had a mean value of 57.7, with a standard deviation of 11.6 (range 34-73); LDH had a mean value of 242.2, with a standard deviation of 32.6 (range 185-293); and Alkaline phosphatase had a mean value of 126, with a standard deviation of 20.4 (range 95-166).The mean value of baseline systolic BP in subjects receiving amlodipine therapy was 132.8 with a standard deviation of 9.4. The mean value of 4-week systolic BP in subjects receiving amlodipine therapy was 127.5 with a standard deviation of 8.3. The mean value of 8-week systolic BP in subjects receiving amlodipine therapy was 123.1 with a standard deviation of 10.2. The mean value of baseline systolic BP in subjects receiving olmesartan therapy was 136.1 with a standard deviation of 10.6. The mean value of 4-week systolic BP in subjects receiving olmesartan therapy was 130.1 with a

standard deviation of 6.8. The mean value of 8-week systolic BP in subjects receiving olmesartan therapy was 124.4 with a standard deviation of 8.4. The mean value of baseline diastolic BP in subjects receiving combination therapy was 100.7 with a standard deviation of 7.5. The mean value of 4-week diastolic BP in subjects receiving combination therapy was 92.4 with a standard deviation of 4.3. The mean value of 8-week diastolic BP in subjects receiving combination therapy was 89.6 with a standard deviation of 5.8.The mean value of baseline diastolic BP in subjects receiving amlodipine therapy was 96.4 with a standard deviation of 9.1. The mean value of 4-week diastolic BP in subjects receiving amlodipine therapy was 93.1 with a standard deviation of 6.5. The mean value of 8-week diastolic BP in subjects receiving amlodipine therapy was 92.5 with a standard deviation of 7.9.

References

[1] Mozaffarian D et al. Heart disease and stroke statistics — 2015 update: A report from the American Heart Association. Circulation 2015; 131: e29-e322.
[2] World Health Organization. Global status reports on Non-Communicable diseases, 2010. [Available on: http://www.who.int/nmh/publications/ncd_report_full_en.pdf].
[3] Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe 2015: An epidemiological update. Eur Heart J 2015; 36: 2673-74.
[4] Global Burden of Diseases 2013 Mortality and Causes of Death Collaborators. Global, regional, and national levels of age -sex specific all -cause Moran AE, Forouzanfar MH, Roth GA, et al.
[5] Fuster V, Kelly BB, and Board for Global Health. Promoting cardiovascular health in developing world: a critical challenge to achieve global health. Washington. Institute of Medicine, 2010.
[6] Gupta R, Guptha S, Sharma KK, et al. Regional variations in cardiovascular risk factors in India: India Heart Watch. World J Cardiol 2012; 4:112-120.
[7] Gupta R, Joshi PP, Mohan V, et al. Epidemiology and causation of coronary heart disease and stroke in India. Heart 2008; 94:16-26.
[8] Rodgers A, Lawes C, MacMahon S. Reducing the global burden of blood pressure related cardiovascular disease. J Hypertens 2000; 18(Suppl 1):S3 -S6.
[9] Patel V, Chatterji S, Chisholm D, et al. Chronic diseases and injuries in India. Lancet 2011; 377:413-428.
[10] Gupta R. Trends in hypertension epidemiology in India. J Hum Hypertens 2004; 18:73-78
[11] Gupta R, Al-Odat NA, Gupta VP. Hypertension epidemiology in India: Meta -analysis of fifty-year prevalence rates and blood pressure trends. J Hum Hypertens 1996; 10:465-472.
[12] Anchala R, Kannuri S, Pant H, et al. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension J Hypertens 2014; 32:1170-77.
[13] Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. Am J Hypertens 2001; 14(3): 241-47.
[14] Chobanian AV, Bakris GL, Black HR, et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung and Blood Institute. National High Blood Pressure Education Program Coordinating Committee Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42(6): 1206-52
[15] Mancia G, De Backer G, Dominiczak A, et al. The task force for the management of arterial hypertension of the European Society of HypertensionWald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combinatory therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122(3):290–300.
[16] Sever PS, Messerli FH. Hypertension management 2011: optimal combination therapy. Eur Heart J 2011;32(20): 2499-2506.
[17] Aulakh GK, Sodhi RK, Singh M. An update of non peptide angiotensin receptor antagonists and related RAAS MODULATORS. Life Sci2007; 81(8): 615-39. doi;10.1016/j.lfs.2007.06.007
[18] Arcangelo, Virginia poole;Peterson, Andrew M. Pharmacotherapeutics for advanced practice: A practical approach, 2006. Lippincott Williams and Wilkins. ISBN: 9780781757843
[19] Vasan R.S., Beiser A., Seshadri S., Larson M.G., Kannel W.B., D'Agostino R.B, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA 2002; 287: 1003-1010
[20] Vasan R.S., Larson M.G., Leip E.P., Kannel W.B, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet 2001; 358: 1682-1686
[21] Carretero O.A, Oparil S. Essential hypertension. Part I: definition and etiology. Circulation 2001; 101, 329-335
[22] Rodriguez-Cruz E, Ettinger L.M. Cardiac Disease and Critical Care Medicine. In eMedicine Pediatrics: Medscape, 2010.
[23] Wofford M.R, Hall J.E. Pathophysiology and treatment of obesity hypertension. Curr Pharm Des 2004; 10, 3621-3637.
[24] Lackland D.T, Egan B.M. Dietary salt restriction and blood pressure in clinical trials. Curr Hypertens Rep 2007; 9, 314-319.
[25] Djousse L, Mukamal K.J. Alcohol consumption and risk of hypertension: does the type of beverage or drinking pattern matter? Rev EspCardiol2009; 62, 603-605.
[26] Lee J.H., O'Keefe J.H., Bell D., Hensrud D.D, Holick M.F. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? J Am CollCardiol 2008; 52, 1949-1956
[27] Tuohimaa P. Vitamin D and aging. J Steroid BiochemMolBiol2009; 114, 78-84
[28] Kosugi T., Nakagawa T., Kamath D, Johnson R.J. Uric acid and hypertension: an age-related relationship? J Hum Hypertens2009; 23, 75-76
[29] Dickson M.E, Sigmund C.D. Genetic basis of hypertension: revisiting angiotensinogen. Hypertension 2006; 48: 14-20
[30] Luma G.B, Spiotta R.T. Hypertension in children and adolescents. Am Fam Physician 2006; 73, 1558-1568
[31] Segura J, Ruilope L.M. Obesity, essential hypertension and renin-angiotensin system. Public Health Nutr2007; 10, 1151-1155
[32] Rahmouni K., Correia M.L., Haynes W.G, Mark A.L. Obesity-associated hypertension: new insights into mechanisms. Hypertension 2005; 45, 9-14
[33] Sorof J, Daniels S. Obesity hypertension in children: a problem of epidemic proportions. Hypertension 2002; 40, 441-447.
[34] Uchiyama M. [Mild hypertension in children]. Nihon Rinsho2008; 66, 1477-1480
[35] Dodt C., Wellhoner J.P., Schutt M., Sayk F. [Glucocorticoids and hypertension]. Internist (Berl) 2009; 50, 36-41.
[36] Bullock B.L. Focus on Pathophysiology. Philadelphia: Lippincott Williams & Wilkins, 2000.
[37] Porth C.M. Pathophysiology; concepts of altered health states, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2002.

[38] Neal B., MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet 2000; 356, 1955-1964

[39] Ogden L.G., He J., Lydick E, Whelton P.K. Long-term absolute benefit of lowering blood pressure in hypertensive patients according to the JNC VI risk stratification. Hypertension 2000; 35, 539-543

[40] Sacks F.M., Svetkey L.P., Vollmer W.M., Appel L.J., Bray G.A., Harsha D., Obarzanek E., Conlin P.R., Miller E.R., 3rd, Simons-Morton D.G., Karanja N. and Lin P.H. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 2001; 344, 3-10

[41] Leiter L.A., Abbott D., Campbell N.R., Mendelson R., Ogilvie R.I. and Chockalingam A. Lifestyle modifications to prevent and control hypertension. 2. Recommendations on obesity and weight loss. CMAJ 1999; 160, S7-12

[42] Cutler J.A., Follmann D, Allender P.S. Randomized trials of sodium reduction: an overview. Am J ClinNutr1997;65, 643S-651S.

[43] Whelton P.K., Appel L.J., Espeland M.A., et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. JAMA 1998; 279, 839-846.

[44] Hagberg J.M., Park J.J, Brown M.D. The role of exercise training in the treatment of hypertension: an update. Sports Med 2000; 30, 193-206

[45] He J., Whelton P.K., Appel L.J., Charleston J, Klag M.J. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. Hypertension 2000; 35, 544-549

[46] Xin X., He J., Frontini M.G., Ogden L.G., Motsamai O.I, Whelton P.K. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension 2001; 38, 1112-1117

[47] Kuncl N, Nelson K.M. Antihypertensive drugs. Nursing 1997; 27, 46-8

[48] Holcomb S.S. Understanding the ins& outs of diuretic therapy. Nursing 1997; 27, 34-40

[49] Anderson P.O., Knoben J.E, Troutman W.G. Handbook of clinical drug data 1999- 2000, 9th ed. New York: McGraw-Hil, 1999.

[50] Morrison R.T. Edema and principles of diuretic use. Med Clin North Am 1997; 81, 689-704

[51] Skidmore-Roth L. Mosby's nursing drug reference. St. Louise: Mosby, 2001

[52] Gilman A., Hardman J.G, Limbird L.E. Goodman and Gilman's the pharmacological basis of therapeutics, 10th ed. New York: McGraw-Hill; 2002.

[53] Karch A.M. Focus on Nursing Pharmacology, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2003.

[54] Galbraith A., Bullock S., Manias E., Hunt B, Richards A. Fundamentals of Pharmacology; an applied approach for nursing and health, 2nd ed. United Kingdom: Pearson Education limited; 2007.

[55] Lilley L.L, Aucker R.S. Pharmacology and the Nursing Process, 3rd ed. St Louise: Mosby; 2001.

[56] Lehne R. Pharmacology for Nursing Care, 7th ed. St. Louis, Missouri: Saunders Elsevier; 2010.

[57] Skidmore-Roth L. Mosby's nursing drug reference. St. Louise: Mosby, 2001.

[58] Nordqvist C., Timpka T, Lindqvist K. What promotes sustainability in Safe Community programmes? BMC Health Serv Res 2009; 9, 4.

[59] TuK., Campbell N.R., Duong-Hua M, McAlister F.A. Hypertension management in the elderly has improved: Ontario prescribing trends, 1994 to 2002. Hypertension 2005; 45, 1113-1118.

[60] Black H.R., Elliott W.J., Grandits G., et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA 2003; 289, 2073-2082.

[61] Kearney P.M., Whelton M., Reynolds K., Whelton P.K, He J. Worldwide prevalence of hypertension: a systematic review. J Hypertens2004; 22, 11-19.

[62] Fagard R.H., Van Den Enden M., Leeman M, Warling X. Survey on treatment of hypertension and implementation of World Health Organization/International Society of Hypertension risk stratification in primary care in Belgium. J Hypertens2000; 20, 1297-1302

[63] Chobanian A.V., Bakris G.L., Black H.R., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289, 2560-2572

[64] Lis A., Prasanth N.V., Sanal D.K.T., Sheeba J., Yousuf K., Shinu C. and Anees T. A study conducted on prescribing pattern and cost of antihypertensive drugs in a tertiary level hospital in South Malabar region of Kerala, India. Der PharmaChemica2010; 2, 332-341

[65] Cheng H. Prescribing pattern of antihypertensive drugs in a general hospital in central China. Int J Clin Pharm 2011; 33, 215-22.

[66] Garjón J, Saiz LC, Azparren A, Elizondo JJ, Gaminde I, Ariz MJ, Erviti J. First-line combination therapy versus first-line monotherapy for primary hypertension. Cochrane Database of Systematic Reviews 2017; DOI: 10.1002/14651858.CD010316.pub2

[67] James PA, Oparil S, Carter BL et al. Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–20.

[68] Niemeijer MG, Cleophas TJ. Combination Therapy with Olmesartan and Amlodipine in the Treatment of Hypertension. Pharmaceuticals. 2009;2(3):125-133. doi:10.3390/ph2030125.

[69] Chrysant S.G., Melino M., Karki S., Lee J., Heyrman R. The combination of olmesartan medoximil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. Clin. Ther. 2008;30:587–604.

[70] Zhang X, Zhang H, Ma Y, Che W, Hamblin MR. Management of Hypertension Using Olmesartan Alone or in Combination. Cardiology and Therapy. 2017;6(1):13-32. doi:10.1007/s40119-017-0087-5.

[71] Derosa G, et al. Different aspects of sartan + calcium antagonist association compared to the single therapy on inflammation and metabolic parameters in hypertensive patients. Inflammation. 2014;37(1):154–162. doi: 10.1007/s10753-013-9724-x.

[72] Derosa G, et al. Effects of an olmesartan/amlodipine fixed dose on blood pressure control, some adipocytokines and interleukins levels compared with olmesartan or amlodipine monotherapies. J Clin Pharm Ther. 2013;38(1):48–55. doi: 10.1111/jcpt.12021.

[73] Sievers P, et al. Combined treatment with olmesartan medoxomil and amlodipine besylate attenuates atherosclerotic lesion progression in a model of advanced atherosclerosis. Drug Des DevelTher. 2015;9:3935–3942.

[74] The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 Guidelines for the management of arterial hypertension. Eur. Heart J. 2007;28:1462–536.

[75] Volpe, P. Brommer, U. Haag, C. MieleEfficacy and tolerability of olmesartan medoxomil combined with amlodipine in patients with moderate to severe hypertension

[76] Chrysant SG, Marbury TC, Silfani TN. Use of 24-h ambulatory blood pressure monitoring to assess blood pressure control: a comparison of olmesartan medoxomil and amlodipine besylate. Blood Press Monit. 2006;11(3):135–141.

[77] Flack JM. Maximising antihypertensive effects of angiotensin II receptor blockers with thiazide diuretic combination therapy: focus on irbesartan/hydrochlorothiazide. International Journal of Clinical Practice. 2007;61(12):2093-2102. doi:10.1111/j.1742-1241.2007.01577.x.
[78] Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the conduit artery function evaluation (cafe) study. Circulation. 2006;113:1213–225.
[79] Stein H. Johnsen, Hallvard Lilleng, Svein I. Bekkelund. Creatine Kinase as Predictor of Blood Pressure and Hypertension. Is It All About Body Mass Index? A Follow-Up Study of 250 Patients. J Clin Hypertens (Greenwich). 2014;16:820–826
[80] Oudman I, Kewalbansingh PV, van Valkengoed I, et al. Creatine kinase is associated with failure of hypertension treatment. J Hypertens. 2013;**31**:1025–1031.
[81] Kavgaci H, Sahin A, OnderErsoz H, Erem C, Ozdemir F. The effects of losartan and fosinopril in hypertensive type 2 diabetic patients. Diabetes Res Clin Pract. 2002;58:19–25. doi: 10.1016/S0168-8227(02)00102-X.

Dr Ankur Sharma. " Evaluation of Safety And Efficacy of A Fixed Olmesartan / Amlodipine Combination Therapy Compared To Single Monotherapies." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 3, 2018, pp 08-21