STUDY OF DRUG PRESCRIPTION PATTERN OF ANTI-HYPERTENSIVES IN A TERTIARY CARE HOSPITAL

A dissertation submitted to

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MASTER OF PHARMACY
IN
PHARMACY PRACTICE

Submitted by

Reg. No. 261240206

Under the guidance of

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled "**Study of drug prescription pattern of anti-hypertensives in a tertiary care hospital"** submitted by the student bearing [**Reg. No: 261240206]** 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……..…….

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This is to certify that the dissertation "**Study of drug prescription pattern of anti-hypertensives in a tertiary care hospital",** is a bonafide work done by **Reg.No.261240206 J.K.K. Nattraja 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.

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DECLARATION

I do hereby declared that the dissertation "**Study of drug prescription pattern of anti-hypertensives in a tertiary care hospital"** 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.N.Venkateswaramurthy., M.Pharm.** 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.

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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".

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1. INTRODUCTION

Worldwide, high blood pressure (HBP) is estimated to cause 7.1 million deaths, about 13 percent of the global fatality total. Across world health organization (WHO) regions, research indicates that about 62 percent of strokes and 49 percent of heart attacks are caused by HBP.[1] Increasing awareness and diagnosis of hypertension and improving control of BP with appropriate treatment are considered critical Public health initiatives to reduce cardiovascular morbidity and mortality. The Seventh Report of the Joint National Committee (JNC7) on the Detection, Evaluation, and Treatment of HBP was developed to aid clinicians in the management of hypertension.[2]

The "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" provides a new guideline for hypertension prevention and management. According to JNC – 7 guidelines in persons older than 50 years, systolic blood pressure greater than 140 mmHg is a much more important cardiovascular disease (CVD) risk factor than diastolic blood pressure.[2]

The WHO estimates that 600 million people with HBP are at risk of heart attack, stroke and cardiac failure. A study of hypertension in six European countries, Canada and the United States showed the average blood pressure (BP) was 136/83 mm Hg in the European countries and 127/77 mm Hg in Canada and the United States, among men and women ages 35–74 years. For all age groups, BP measurements were lowest in the United States and highest in Germany.[1] Worldwide, Indo-Asian people are among the populations at highest risk for cardiovascular disease.[3] Evidence also suggests that associations between body mass index (BMI), percentage of body fat and chronic disease may differ between Indo-Asian and European populations.[4,5] Because of the observed differences between populations, the International Association for the Study of Obesity and the International Obesity Task Force have suggested lower BMI cutoff values for the definitions of overweight (23.0–24.9 kg/m^2) and obesity (25.0 kg/m^2 or greater) in Asian populations.[6]

Dubey VD[7] carried out one of the earliest study in India (1954), documented 4% prevalence of hypertension (criteria:>160/95) amongst industrial workers of Kanpur. During 1984-87 Gopinath and Chadha[8,9] *et al*., reported the prevalence of hypertension in Delhi

(criteria: ≥160/90) to be 11% among males and 12% among females in the urban areas and 4% and 3% respectively in rural areas. Another two studies carried out in rural areas of Haryana[10] (1994-95) demonstrated 4.5% prevalence of hypertension (JNC V criteria) while urban areas of Delhi had a higher prevalence of 45% during 1996-97.[11] Few studies were carried out comparing different socio economic groups. The initial study from urban Chennai, Mohan[12] *et al*., reported 8.4% prevalence of hypertension among men and women aged 20 years and above and belonging to the low socio economic group (based on household income, occupation and dietary pattern). Similarly, in the middle socio economic group had a higher prevalence (15%) during 1996-97. A study conducted in the urban areas of Chennai during 2000[13] (age group ≤ 40) reported a higher prevalence of hypertension (54%) among low income group (monthly income < Rs 30000/annum and 40% prevalence among high-income group (monthly income ≤ Rs 60000/annum). Misra[14] *et al*., reported 12% prevalence of hypertension in the slums of Delhi. From south India, Kutty VR[15] carried out hypertension prevalence study (criteria: ≤ 160/95 mm of Hg) in rural Kerala during 1991 in the 20 plus age group and the prevalence was found to be 18%. Later studies in Kerala (Criteria: JNC VI) reported 37% prevalence of hypertension among 30-64 age group[16] in 1998 and 55% among 40-60 age group[17] during 2000. A higher prevalence of 69% and 55% was recorded among elderly populations aged sixty and above in the urban and rural areas respectively during 2000.[18]

Interactions between genetic and hemodynamic factors cause hypertensive heart disease in patients with arterial hypertension. The resulting structural and functional adaptations lead to increased left ventricular (LV) mass, diastolic dysfunction, congestive heart failure (CHF), arrhythmias and abnormalities of myocardial perfusion due to microvascular endothelial dysfunction. Consequently, hypertensive individuals with hypertensive heart disease are more prone to myocardial infarction, congestive heart failure, stroke, and sudden death then persons with hypertension alone. [19]

1.1 HYPERTENSION

Hypertension is a common disease that is defined simply as persistently elevated arterial blood pressure (BP). Increasing awareness and diagnosis of hypertension and improving control of BP with appropriate treatment are considered critical Public health

initiatives to reduce cardiovascular morbidity and mortality. It is a heterogeneous medical condition. In most patients it results from unknown pathophysiologic etiology (essential or primary hypertension). While this form of hypertension cannot be cured, it can be controlled. A small percentage of patients have a specific cause of their hypertension (secondary hypertension). It is defined simply as persistently elevated arterial BP. The JNC7 classification of BP in adults (age $\geq$ 18 years) is based on the average of two or more properly measured BP readings from two or more clinical encounters[2]. It includes four categories, with normal values considered to be a systolic blood pressure (SBP) of less than 120 mm Hg and a diastolic blood pressure (DBP) of less than 80mmHg. Prehypertension is not considered a disease category but identifies patients whose BP is likely to increase into the classification of hypertension in the future. There are two stages of hypertension, and all patients in these categories need drug therapy.

Table. 1 Classification of Blood Pressure in Adults (Age ≥ 18 Years) [a]

Classification	Systolic BP(mmHg)	Diastolic BP(mmHg)
Normal	Less than 120	Less than 80
Prehypertension[b]	120-139	80-89
Stage 1hypertension	140-159	90-99
Stage 2hypertension	Greater than or equal to 160	Greater than or equal to 100

a Classification determined based on the average of two or more properly measured seated BP measurements from two or more clinical encounters. If systolic and diastolic blood pressure values yield different classifications, the highest category is used for the purpose of determining a classification.

b For patients with diabetes mellitus or chronic kidney disease, values $\leq$130/80 mm Hg are considered above goal.

1.2. ETIOLOGICAL CLASSIFICATION

In most patients it results from unknown pathophysiologic etiology (essential or primary hypertension). While this form of hypertension cannot be cured, it can be controlled.

A small percentage of patients have a specific cause of their hypertension (secondary hypertension). There are many potential secondary causes that are either concurrent medical conditions or are endogenously induced. If the cause of secondary hypertension can be identified, hypertension in these patients potentially can be cured.

1.2.1 Primary hypertension

Over 90% of individuals with hypertension have essential hypertension (primary hypertension).[2] Numerous mechanisms have been identified that may contribute to the pathogenesis of this form of hypertension, so identifying the exact underlying abnormality is not possible. Hypertension often runs in families, indicating that genetic factors may play an important role in the development of essential hypertension. Data suggest that there are monogenic and polygenic forms of BP dysregulation that may be responsible for essential hypertension. Many of these genetic traits feature genes that affect sodium balance, but genetic mutations altering urinary kallikrein excretion, nitric oxide release, aldosterone excretion, other adrenal steroids, and angiotensinogen are also documented.[20]

1.2.2 Secondary hypertension

Some additional signs and symptoms may suggest secondary hypertension, i.e. hypertension due to an identifiable cause such as kidney diseases or endocrine diseases. For example, truncal obesity, glucose intolerance, moon face, a "buffalo hump" and purple stretch marks suggest Cushing's syndrome.[5] Thyroid disease and acromegaly can also cause hypertension and have characteristic symptoms and signs.[5] An abdominal bruit may be an indicator of renal artery stenosis (a narrowing of the arteries supplying the kidneys), while decreased blood pressure in the lower extremities and/or delayed or absent femoral arterial pulses may indicate aortic coarctation (a narrowing of the aorta shortly after it leaves the heart). Labile or paroxysmal hypertension accompanied by headache, palpitations, pallor, and perspiration should prompt suspicions of pheochromocytoma.[5]

Hypertensive crisis

Severely elevated blood pressure (equal to or greater than a systolic 180 or diastolic of 110 — sometimes termed malignant or accelerated hypertension) is referred to as a

"hypertensive crisis", as blood pressures above these levels are known to confer a high risk of complications. People with blood pressures in this range may have no symptoms, but are more likely to report headaches (22% of cases)[6] and dizziness than the general population.[2] Other symptoms accompanying a hypertensive crisis may include visual deterioration or breathlessness due to heart failure or a general feeling of malaise due to renal failure.[5] Most people with a hypertensive crisis are known to have elevated blood pressure, but additional triggers may have led to a sudden rise.[7]

A "hypertensive emergency", previously "malignant hypertension", is diagnosed when there is evidence of direct damage to one or more organs as a result of the severely elevated blood pressure. This may include hypertensive encephalopathy, caused by brain swelling and dysfunction, and characterized by headaches and an altered level of consciousness (confusion or drowsiness). Retinal papilloedema and/or fundal hemorrhages and exudates are another sign of target organ damage. Chest pain may indicate heart muscle damage (which may progress to myocardial infarction) or sometimes aortic dissection, the tearing of the inner wall of the aorta. Breathlessness, cough, and the expectoration of blood-stained sputum are characteristic signs of pulmonary edema, the swelling of lung tissue due to left ventricular failure an inability of the left ventricle of the heart to adequately pump blood from the lungs into the arterial system.[7] Rapid deterioration of kidney function (acute kidney injury) and microangiopathic hemolytic anemia (destruction of blood cells) may also occur.[7] In these situations, rapid reduction of the blood pressure is mandated to stop ongoing organ damage.[7] In contrast there is no evidence that blood pressure needs to be lowered rapidly in hypertensive urgencies where there is no evidence of target organ damage and over aggressive reduction of blood pressure is not without risks.[5] Use of oral medications to lower the BP gradually over 24 to 48h is advocated in hypertensive urgencies.[7]

1.3 DIAGNOSIS

Essential hypertension is usually asymptomatic. The primary physical finding is elevated BP. The diagnosis of hypertension cannot be made based on one elevated BP measurement. The average of two or more measurements taken during two or more clinical encounters should be used to diagnose hypertension.[2] Thereafter, this BP average can be used to establish a diagnosis and then to classify the stage of hypertension present in the patient.

1.3.1 Measuring blood pressure

1.3.1.1 *Sphygmomanometry*

Indirect measurement of BP using a sphygmomanometer is a common routine medical screening tool that should be conducted at every health care encounter.[20] The appropriate procedure to measure BP has been described by the American Heart Association (AHA).[22] It is imperative that the measurement equipment (inflation cuff, stethoscope, manometer) meet certain national standards.[23] These standards use criteria to ensure maximum quality and precision with measurement.

1.4. PATHOPHYSIOLOGY[20,24]

A clear understanding of arterial BP and regulation is needed to manage hypertension appropriately and to understand antihypertensive drug therapy mechanistically. Multiple factors that control BP are potential contributing components in the development of hypertension. These include malfunctions in either humoral (i.e., the renin-angiotensin-aldosterone system [RAAS]) or vasodepressor mechanisms, abnormal neuronal mechanisms, defects in peripheral autoregulation, and disturbances in sodium, calcium, and natriuretic hormone. Many of these factors are cumulatively affected by the multifaceted RAAS, which ultimately regulates arterial BP.

1.4.1 Potential mechanisms of pathogenesis

Blood pressure is the mathematical product of cardiac output and peripheral resistance. Increased blood pressure can result from increased cardiac output and/or increased total peripheral resistance.

Table.3

Increased cardiac output	**Increased peripheral resistance**
Increased cardiac preload: ▪ Increased fluid volume from excess sodium intake or renal sodium retention (from reduced number of nephrons or decreased glomerular filtration) Venous constriction: ▪ Excess stimulation of the RAAS ▪ Sympathetic nervous system overactivity	Functional vascular constriction: ▪ Excess stimulation of the RAAS ▪ Sympathetic nervous system overactivity ▪ Genetic alterations of cell membranes ▪ Endothelial-derived factors Structural vascular hypertrophy: ▪ Excess stimulation of the RAAS ▪ Sympathetic nervous system overactivity ▪ Genetic alterations of cell membranes ▪ Endothelial-derived factors ▪ Hyperinsulinemia resulting from obesity or the metabolic syndrome

1.4.2 Humoral mechanisms

Several humoral abnormalities may be involved in the development of essential hypertension. These abnormalities may involve the the renin-angiotensin-aldosterone system, natriuretic hormone and hyperinsulinemia.

1.4.2.1 *The renin-angiotensin-aldosterone system (RAAS)*

The RAAS is a complex endogenous system that is involved with most regulatory components of arterial BP. Activation and regulation are governed primarily by the kidney. The RAAS regulates sodium, potassium, and fluid balance. Therefore, this system

significantly influences vascular tone and sympathetic nervous system activity and is the most influential contributor to the homeostatic regulation of BP. Renin is an enzyme that is stored in the juxtaglomerular cells, which are located in the afferent arterioles of the kidney. The release of renin is modulated by several factors: intrarenal factors (e.g., renal perfusion pressure, catecholamines, and angiotensin II) and extrarenal factors (e.g., sodium, chloride, and potassium).

Renin catalyzes the conversion of angiotensinogen to angiotensin I in the blood. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE). After binding to specific receptors (classified as either AT_1 or AT_2 subtypes), angiotensin II exerts biologic effects in several tissues. The AT1 receptor is located in brain, kidney, myocardium, peripheral vasculature, and the adrenal glands. These receptors mediate most responses that are critical to cardiovascular and kidney function. The AT_2 receptor is located in adrenal medullary tissue, uterus, and brain. Stimulation of the AT_2 receptor does not influence BP regulation. Circulating angiotensin II can elevate BP through pressor and volume effects. The pressor effects include direct vasoconstriction, stimulation of catecholamine release from the adrenal medulla, and centrally mediated increases in sympathetic nervous system activity. Angiotensin II also stimulates aldosterone synthesis from the adrenal cortex. This leads to sodium and water reabsorption that increases plasma volume, total peripheral resistance, and ultimately, BP.

1.4.2.2 *Natriuretic hormone*

Natriuretic hormone inhibits sodium and potassium ATPase and thus interferes with sodium transport across cell membranes. Inherited defects in the kidney's ability to eliminate sodium can cause an increased blood volume. A compensatory increase in the concentration of circulating natriuretic hormone theoretically could increase urinary excretion of sodium and water. However, this same hormone is also thought to block the active transport of sodium out of arteriolar smooth muscle cells. The increased intracellular concentration of sodium ultimately would increase vascular tone and BP.

1.4.2.3 *Insulin resistance and hyperinsulinemia*

Increased insulin concentrations may lead to hypertension because of increased renal sodium retention and enhanced sympathetic nervous system activity. Moreover, insulin has growth hormone–like actions that can induce hypertrophy of vascular smooth muscle cells. Insulin also may elevate BP by increasing intracellular calcium, which leads to increased vascular resistance. The exact mechanism by which insulin resistance and hyperinsulinemia occur in hypertension is unknown. However, this association is strong because many of the criteria used to define this population (elevated blood pressure, obesity, dyslipidemia, and elevated blood glucose) are often present in hypertensive patients.[20]

1.4.3 Neuronal regulation

The central and autonomic nervous systems are intricately involved in the regulation of arterial BP. A number of receptors that either enhance or inhibit norepinephrine release are located on the presynaptic surface of sympathetic terminals. The α and β presynaptic receptors play a role in negative and positive feedback to the norepinephrine containing vesicles located near the neuronal ending. Stimulation of presynaptic α-receptors ($\alpha 2$) exerts a negative inhibition on norepinephrine release. Stimulation of presynaptic □-receptors facilitates further release of norepinephrine. Sympathetic neuronal fibers located on the surface of effector cells innervate α-receptors ($\alpha 2$). Stimulation of postsynaptic α-receptors ($\alpha 2$) on arterioles and venules results in vasoconstriction. There are two types postsynaptic β-receptors, β1 and β2.. Both are present in all tissue innervated by the sympathetic nervous system. However, in some tissues, β1-receptors predominate, and in other tissues, β2-receptors predominate. Stimulation of $\beta 1$-receptors in the heart results in an increase in heart rate and contractility, whereas stimulation of $\beta 2$-receptors in the arterioles and venules causes vasodilation.

1.4.4 Peripheral autoregulatory components

Abnormalities in renal or tissue autoregulatory systems could cause hypertension. It is possible that a renal defect in sodium excretion may develop first, which can then cause resetting of tissue autoregulatory processes, resulting in a higher arterial BP. The kidney usually maintains normal BP through a volume-pressure–adaptive mechanism. When BP drops, the kidneys respond by increasing retention of sodium and water. These changes lead to plasma volume expansion, which increases BP. Conversely, when BP rises above normal, renal sodium and water excretion are increased to reduce plasma volume and cardiac output. This ultimately will maintain homeostatic BP conditions.

1.4.5 Vascular endothelial mechanisms

Vascular endothelium and smooth muscle play important roles in regulating blood vessel tone and BP. These regulating functions are mediated through vasoactive substances that are synthesized by endothelial cells. It has been postulated that a deficiency in the local synthesis of vasodialating substances (e.g., prostacyclin and bradykinin) or excess vasoconstricting substances (e.g., angiotensin II and endothelin I) contribute to essential hypertension, atherosclerosis, and other diseases. Nitric oxide is produced in the endothelium, relaxes the vascular epithelium, and is a very potent vasodilator. The nitric oxide system is an important regulator of arterial BP. Hypertensive patients may have an intrinsic deficiency in nitric oxide release, resulting in inadequate vasodilatation. Although the exact role of nitric oxide in hypertension is unclear, it may be a pharmacologic target in the future.

1.4.6 Electrolytes and other chemicals

Epidemiologic and clinical data have associated excess sodium intake with hypertension. Population-based studies indicate that high-salt diets are associated with a high prevalence of stroke and hypertension. Conversely, low-salt diets are associated with a low prevalence of hypertension. Clinical studies have shown consistently that dietary sodium restriction lowers BP in many (but not all) patients with elevated BP.

Altered calcium homeostasis also may play an important role in the pathogenesis of hypertension. A lack of dietary calcium hypothetically can disturb the balance between

intracellular and extracellular calcium, resulting in an increased intracellular calcium concentration. This imbalance can alter vascular smooth muscle function by increasing peripheral vascular resistance.

In the case of potassium, Potassium depletion may increase peripheral vascular resistance, but the clinical significance of small serum potassium concentration changes is unclear. Furthermore, data demonstrating reduced cardiovascular risk with dietary potassium supplementation are very limited.

1.5. TREATMENT[20]

1.5.1 Goal of therapy

The overall goal of treating hypertension is to reduce hypertension-associated morbidity and mortality.[2] This morbidity and mortality are related to target-organ damage (e.g., cardiovascular events, cerebrovascular events, heart failure, and kidney disease). Reducing risk remains the primary purpose of hypertension therapy, and the choice of drug therapy is influenced significantly by evidence demonstrating such risk reduction.

1.5.2 General approach to treatment

Hypertension is one of the most common medical conditions, BP control rates are poor. Many hypertensive patients are at goal DBP values but continue to have elevated SBP values. It has been estimated that of the hypertensive population that is treated yet not controlled, 76.9% have an SBP greater than or equal to 140 mm Hg with DBP values less than 90 mm Hg.[25]

The diaganosed patient should be placed on both lifestyle modifications and drug therapy concurrently. Lifestyle modification alone is considered appropriate therapy for patients with prehypertension. However, lifestyle modifications alone are not considered adequate for patients with hypertension or patients with BP goals of less than 130/80 mm Hg (those with diabetes and chronic kidney disease) who have BP values above their goal.

1.5.3 Nonpharmacologic therapy

All patients with prehypertension and hypertension should be prescribed lifestyle modifications. These approaches are recommended by the JNC7[2] and provide small to moderate reductions in SBP. Aside from lowering BP in patients with known hypertension, lifestyle modification can decrease the progression to hypertension in patients with prehypertension BP values.[26] In a number of hypertensive patients with relatively good BP control while on single antihypertensive drug therapy, sodium reduction and weight loss may allow withdrawal of drug therapy.[27,28]

A sensible dietary program is one that is designed to reduce weight gradually for overweight and obese patients and one that restricts sodium intake with only moderate alcohol consumption. Successful implementation of dietary lifestyle modifications by clinicians requires aggressive promotion through reasonable patient education, encouragement, and continued reinforcement. Patients may better understand the rationale for dietary intervention in hypertension if they are provided the following observations and facts:

1. Hypertension is two to three times more prevalent in overweight as compared with lean persons.
2. Over 60% of hypertensive persons are overweight.
3. Weight loss, even as little as 10 pounds, can decrease BP significantly in hypertensive overweight individuals.[29]
4. Abdominal obesity is associated with the metabolic syndrome, which is a precursor to hypertension and insulin-resistance syndrome that may progress to type 2 diabetes, dyslipidemia, and ultimately, cardiovascular disease.[30]
5. Diets rich in fruits and vegetables and low in saturated fat have been shown to lower BP in hypertensive individuals.[31,32]
6. Although some hypertensive patients are not salt-sensitive, most people experience some degree of SBP reduction with sodium restriction.[20,33]

A controlled diet plan is needed that is rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat. The recommended restriction is less than 2.4 g (100 mEq) sodium per day. Patients should be aware of the multiple sources of dietary sodium (e.g., processed meats, soups, and table salt) so that they may follow this

restriction. Excessive alcohol use can either cause or worsen hypertension. Carefully designed programs of physical activity can lower BP. Regular aerobic exercise for at least 30 minutes a day most days of the week is ideal for most patients.

1.5.4 Pharmacologic therapy

There are nine different antihypertensive drug classes. Diuretics, □-blockers, ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers are considered primary antihypertensive agents. These agents, either alone or in combination, should be used to treat the majority of hypertensive patients because evidence from outcomes data have demonstrated benefits with these classes. Several of these classes (i.e., diuretics, □-blockers, and calcium channel blockers) have subclasses where significant differences in mechanism of action, clinical use, or side effects or evidence from outcomes studies exist. □-Blockers, central □ 2-agonists, adrenergic inhibitors, and vasodilators are considered alternative drug classes that may be used in select patients after primary agents.

According to JNC7 guidelines thiazide-type diuretics whenever possible as first-line therapy for most patients.[2] This recommendation is specifically for those without compelling indications and is based on the best available evidence demonstrating reductions in morbidity and mortality. However, diuretics are also useful agents in hypertensive patients with compelling indications, but they are not always the first agent recommended based on the compelling indication present.

Table.4 Primary antihypertensive agents

Class	Subclass	Drug	Usual Dose Range, mg/day
Diuretics	Thiazides	Chlorthalidone	6.25–25
		Hydrochlorothiazide	12.5–50
		Indapamide	1.25–2.5
		Metolazone	0.5
	Loop diuretics	Loops Bumetanide	0.5–4
		Furosemide	20–80
		Torsemide	5
	Potassium sparing	Amiloride	5–10
		Amiloride/ Hydrochlorothiazide	5–10/50–100
		Triamterene	50–100
		Triamterene/ Hydrochlorothiazide	37.5–75/25–50
	Aldosterone Antagonists	Eplerenone	50–100
		Spironolactone	25–50
		Spironolactone/ Hydrochlorothiazide	25–50/25–50
Angiotensin converting enzyme inhibitors		Benazepril	10–40
		Captopril	12.5–150
		Enalapril	5–40
		Fosinopril	10–40
		Lisinopri	10–40
		Moexipril	7.5–30
		Perindopril	4–16
		Quinapril	10–80
		Ramipril	2.5–10

		Trandolapril	1–4
Angiotensin II receptor Blockers		Candesartan	8–32
		Eprosartan	600–800
		Irbesartan	150–300
		Losartan	50–100
		Olmesartan	20–40
		Telmisartan	20–80
		Valsartan	80–320
β-Blockers	Cardioselective	Atenolol	25–100
		Betaxolol	5–20
		Bisoprolol	2.5–10
		Metoprolol	50–200
		Nebivolol	2.5-5
	Nonselective	Nadolol	40–120
		Propranolol	80–320
		Timolol	10–40
	Intrinsic sympathomimetic activity	Acebutolol	200–800
		Carteolol	2.5–10
		Penbutolol	10–40
		Pindolol	10–60
	Mixed □- and □-blockers	Carvedilol	12.5–50
		Labetolol	200–800
Calcium channel blockers	Dihydropyridines	Amlodipine	2.5–10
		Felodipine	5–20
		Isradipine	5–10
		Nicardipine	60–120
		Nifedipine	30–90
		Nisoldipine	10–40
	Non-Dihydropyridines	Diltiazem	180–360
		Verapamil	180–480

Table.5 Alternative antihypertensive agents

Class	Drug	Usual Dose Range, mg/day
α1-Blockers	Doxazosin	1–8
	Prazosin	2–20
	Terazosin	1–20
Central α 2-agonists	Clonidine	0.1–0.8
	Methyldopa	250–1000
Peripheral adrenergic antagonist	Reserpine	0.05–0.25
Direct arterial vasodilators	Minoxidil	10–40
	Hydralazine	20–100

1.5.4.1 *Individual antihypertensive agents*[2,29,34]

Diuretics

Diuretics, preferably a thiazide, are fist-line agents for most patients with hypertension. Moreover, when combination therapy is needed in hypertension to control BP, a diuretic is recommended as one of the agents used.[2] Four subclasses of diuretics are used in the treatment of hypertension: thiazides, loop diuretics, potassium-sparing agents, and aldosterone antagonists Thiazide diuretics have additional actions that may further explain their antihypertensive effects. Thiazides mobilize sodium and water from arteriolar walls. This effect would lessen the amount of physical encroachment on the lumen of the vessel created by excessive accumulation of intracellular fluid. As the diameter of the lumen relaxes and increases, there is less resistance to the flow of blood, and peripheral vascular resistance drops further. Thiazides also are postulated to cause direct relaxation of vascular smooth muscle.

Angiotensin-converting enzyme inhibitors (ACEI)

ACE inhibitors are considered second-line therapy to diuretics in most patients with hypertension.[2] ACE inhibitors have many roles for patients with hypertension and coexisting conditions. ACE facilitates the production of angiotensin II, which has a major role in the regulation of arterial BP. ACE is distributed in many tissues and is present in several different cell types, but its principal location is in endothelial cells. Therefore, the major site for angiotensin II production is in the blood vessels, not the kidney. ACE inhibitors block the conversion of angiotensin I to angiotensin II. This latter substance is a potent vasoconstrictor that also stimulates aldosterone secretion. ACE inhibitors also block the degradation of bradykinin and stimulate the synthesis of other vasodilating substances, including prostaglandin and prostacyclin. The observation that ACE inhibitors lower BP in patients with normal plasma rennin activity suggests that bradykinin and perhaps tissue production of ACE are important in hypertension. Increased bradykinin enhances the BP-lowering effects of ACE inhibitors.

Angiotensin II receptor blockers

Angiotensin II is generated by two enzymatic pathways: the RAAS, which involves ACE, and an alternative pathway that uses other enzymes such as chymases. ACE inhibitors inhibit only the effects of angiotensin II produced through the RAAS, whereas ARBs inhibit angiotensin II from all pathways. It is unclear howthese differences affect tissue concentrations of ACE. Because of these differences, ACE inhibitors only partially block the effects of angiotensin II. ARBs directly block the angiotensin II type 1 (AT_1) receptor that mediates the known effects of angiotensin II in humans: vasoconstriction, aldosterone release, sympathetic activation, antidiuretic hormone release, and constriction of the efferent arterioles of the glomerulus. They do not block the angiotensin II type 2 (AT_2) receptor. Therefore, beneficial effects of AT_2 receptor stimulation (i.e., vasodilation, tissue repair, and inhibition of cell growth) remain intact when ARBs are used. Unlike ACE inhibitors, ARBs do not block the breakdown of bradykinin. Therefore, some of the beneficial effects of bradykinin such as vasodilation (which can enhance BP lowering), regression of myocyte hypertrophy and fibrosis, and increased levels of tissue plasminogen activator are not present with ARB therapy.

Calcium channel blockers (CCB)

CCBs are not first-line agents but are very effective antihypertensive agents, especially in African-American patients. They have compelling indications in high coronary disease risk and in diabetes. However, with these compelling indications, they are in addition to or in replacement of other antihypertensive drug classes. Some data indicated that dihydropyridines may not provide as much protection against cardiac events when compared with "conventional" therapy (diuretics and *β*-blockers) or ACE inhibitors in uncomplicated hypertension.[35] Contraction of cardiac and smooth muscle cells requires an increase in free intracellular calcium concentrations from the extracellular fluid. When cardiac or vascular smooth muscle is stimulated, voltage-sensitive channels in the cell membrane are opened, allowing calcium to enter the cells. The influx of extracellular calcium into the cell releases stored calcium from the sarcoplasmic reticulum. As intracellular free calcium concentration increases, it binds to a protein, calmodulin, which then activates myosin kinase, enabling myosin to interact with actin to induce contraction. CCBs work by inhibiting influx of calcium across the cell membrane. There are two types of voltage-gated calcium channels: a high-voltage channel (L-type) and a low-voltage channel (T-type). Currently available CCBs only block the L-type channel, which leads to coronary and peripheral vasodilation.

β-blockers

β -Blockers have been used in several large outcome trials in hypertension. Several mechanisms of action have been proposed for *β* -adrenoceptor blockers (*β* -blockers), but none of them alone has been shown to be associated consistently with a reduction in arterial BP. *β*-Blockers have negative chronotropic and inotropic cardiac effects that reduce cardiac output, which explains some of the antihypertensive effect. However, cardiac output falls equally in patients treated with *β*-blockers regardless of BP lowering. *β*-Blockers that possess a greater affinity for *β*1-receptors than *β*2-receptors are *cardioselective.* Both *β*1- and *β* 2-adrenoceptors are distributed throughout the body, but they concentrate differently in certain organs and tissues. There is a preponderance of *β* 1- ceptors in the heart and kidney and a preponderance of *β* 2-receptors in the lungs, liver, pancreas, and arteriolar smooth muscle. *β* 1-Receptor stimuation increases heart rate, contractility, and renin release. *β* 2-Receptor

stimulation results in bronchodilation and vasodilation. Cardioselective β -blockers are less likely to provoke bronchospasm and vasoconstriction.

α 1-Blockers

They work in the peripheral vasculature and inhibit the uptake of catecholamines in smooth muscle cells, resulting in vasodilation and BP lowering.

Central α 2-agonists

These agents lower BP primarily by stimulating α 2-adrenergic receptors in the brain. This stimulation reduces sympathetic outflow from the vasomotor center in the brain and increases vagal tone. It is also believed that peripheral stimulation of presynaptic α 2-receptors may further reduce sympathetic tone. Reduced sympathetic activity, together with enhanced parasympathetic activity, can decrease heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor reflexes.

1.6 DRUG UTILIZATION STUDIES[36]

Drug utilization research was defined by WHO as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences".[37]

Studies on the process of drug utilization focus on the factors related to the prescribing, dispensing, administering, and taking of medication, and its associated events, covering the medical and non-medical determinants of drug utilization, the effects of drug utilization, as well as studies of how drug utilization relates to the effects of drug use, beneficial or adverse.[38,39] The therapeutic practice is expected to be primarily based on evidence provided by pre marketing clinical trials, but complementary data from post marketing period are needed to provide an adequate basis for improving drug therapy.[40]

1.6.1 Pharmacoepidemiology

Pharmacoepidemiology applies epidemiological methods to studies of the clinical use of drugs in populations. A modern definition of pharmacoepidemiology is: "the study of the use and effects/side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes".

Pharmacoepidemiology may be drug-oriented, emphasizing the safety and effectiveness of individual drugs or groups of drugs, or utilization oriented aiming to improve the quality of drug therapy through pedagogic (educational) intervention. Drug utilization research may also be divided into descriptive and analytical studies. The emphasis of the former has been to describe patterns of drug utilization and to identify problems deserving more detailed studies. Analytical studies try to link data on drug utilization to figures on morbidity, outcome of treatment and quality of care with the ultimate goal of assessing whether drug therapy is rational or not. Sophisticated utilization-oriented pharmacoepidemiology may focus on the drug (e.g. dose-effect and concentration-effect relationships), the prescriber (e.g. quality indices of the prescription), or the patient (e.g. selection of drug and dose, and comparisons of kidney function, drug metabolic

phenotype/genotype, age, etc.).Drug utilization research is thus an essential part of pharmacoepidemiology as it describes the extent, nature and determinants of drug exposure.

1.6.2 Scope of drug utilization studies

Drug utilization studies may include descriptive epidemiological approaches to the study of drug utilization, but also the assessment of how drug utilization relates to the effects of drug use, beneficial or adverse. The research in this field aims to analyse the present state and the developmental trends, of drug usage at various levels of the health care system, whether national, regional, local or institutional. Drug utilization studies may evaluate drug use at a population level, according to age, sex, social class, morbidity, among other characteristics. These studies are useful to provide denominators to calculate rates of reported adverse drug reactions, to monitor the utilization of drugs from therapeutic categories where particular problems can be anticipated (*e.g.*, narcotic analgesics, hypnotics and sedatives, and other psychotropic drugs), to monitor the effects of informational and regulatory activities (e.g., adverse events alerts, monitoring urgent safety restrictions). Drug utilization data may me used to produce crude estimates of disease prevalence (e.g., cardiovascular disease, antidiabetic drugs, to plan drug importation, production, and distribution, and to estimate drug expenditures.

The characterization of drug utilization may be extended linking prescription data to the reasons for the drug prescribing. They include the concept of appropriateness that must be assessed relative to indication for treatment, concomitant diseases (that might contraindicate or interfere with chosen therapy) and the use of other drugs (interactions). Therefore they can document the extent of inappropriate prescribing of drugs (*e.g.* antibiotics, NSAIDs) and even the associated adverse clinical, ecological, and economic consequences. Moreover, they can also explore the percentage of drugs that adhere to the evidence-based recommendations in place for its indications.

1.6.3 Importance of drug utilization studies

The principal aim of drug utilization research is to facilitate rational use of drugs in populations. For the individual patient rational use of a drug implies the prescription of a well-documented drug in an optimal dose on the right indication, with the correct information and at an affordable price. Without knowledge on how drugs are being prescribed and used, it is difficult to initiate a discussion on rational drug use and to suggest measures to change prescribing habits for the better. Information on the past performance of prescribers is the linchpin of any auditing system.

Drug utilization research in itself does not necessarily provide answers, but it contributes to rational drug use in three important ways:

1.6.3.1 *Description of drug use patterns*

Drug utilization research will increase our understanding of how drugs are being used by:

a. Making estimates of the numbers of patients exposed to drugs within a given time period. Such estimates may either refer to all drug users, regardless of when they started to use the drug (prevalence), or focus on patients who started to use the drug within the selected period (incidence).
b. Describing the extent of use at a certain moment and/or in a certain area (e.g. country, region, community, hospital). Such descriptions are most meaningful when they are part of a continuous evaluation system, i.e. when the patterns are followed over time and trends in drug use can be described.
c. Estimating (e.g. on the basis of epidemiological data on a disease) to what extent drugs are properly used, overused, or underused.
d. Describing the pattern or profile of drug use - assessing which alternative drugs are being used for particular conditions and to what extent.
e. Comparing observed patterns of drug use with current recommendations or guidelines for the treatment of a certain disease.
f. Applying quality indicators to drug utilization patterns. An example is the so-called DU90% (drug utilization 90%), a further development of the “Top-10” list. The

DU90% segment reflects the number of drugs that account for 90% of drug prescriptions and adherence to local or national prescription guidelines in this segment. This general indicator can be applied at different levels (individual prescriber, group of prescribers, hospitals, region, county, etc.) to get a rough estimate of the quality of prescribing.

g. Feeding back drug utilization data to prescribers. This is particularly useful when the individual's drug prescribing can be compared with some form of "gold standard" or best practice, and with the average prescriptions in the country or the area.
h. Relating the number of case reports about a drug problem or adverse effects to the number of patients exposed in order to assess the potential magnitude of the problem. If it is possible to detect that the reaction is more common in a certain age group, in certain conditions or at a special dose level, improving the information on proper use such as indications, contraindications and appropriate dosages may be sufficient to assure a safer use. Thereby withdrawal of the drug from the market may be avoided.

1.6.3.2 *Early signals of irrational use of drugs*

Drug utilization research may generate hypotheses that set the agenda for further investigations by:

a. Comparing drug utilization patterns and costs between different regions or time periods. Hypotheses can be generated to form the basis for investigations of the reasons for, and health implications of, the differences found. Geographical differences and changes overtime in drug use may have medical, social and economic implications both for the individual patient and for society, and are thus important to identify, explain and sometimes correct.
b. Comparing observed patterns of drug use with current recommendations guidelines for the treatment of a certain disease. Hypotheses can then be generated about whether discrepancies represent less than optimal practice, whether pedagogic interventions (education) are required, or whether the guidelines need to be reviewed in the light of actual practice. These considerations should include both underuse and overuse of drugs.

1.6.3.3 *Interventions to improve drug use – follow-up*

Drug utilization research may enable us to assess whether interventions undertaken to improved drug use have had the desired impact by:

a. Monitoring and evaluating the effects of measures taken to improve undesirable patterns of drug use (regional formularies, information, regulatory policies, etc.)
b. Following the impact of regulatory changes or changes in insurance or reimbursement systems. This also requires a broad survey, because the total cost to society may remain the same or may even increase, if other more expensive drugs are used as an alternative.
c. Assessing to which extent promotional activities of the pharmaceutical industry and educational activities of the society impact on the patterns of drug use.

1.6.4 Types of drug use informations

Different types of drug use information are required depending on the problem being evaluated. These include information about the overall drug use, or use of drug groups, individual generic compounds or specific products. Often, information about the condition being treated, about the patient and about the prescriber will be required. In addition, data on drug costs will be important in ensuring that drugs are used efficiently and economically. These types of drug information are described below.

1.6.4.1 *Drug based information*

The trends in total drug use may sometimes be useful to know, but more detailed information is usually required to answer clinically important questions. This may involve aggregation of drug use at various levels, and information on indications, doses and dosage regimens.

1.6.4.2 *Problem or encounter-based information*

Instead of asking how a particular group of drugs is used, one may well address the question how a particular problem (e.g. sore throat, hypertension, gastric ulcer, depression) is managed.

1.6.4.3 *Patient information*

Demographic and other information about the patient will often be useful. The age distribution of patients will sometimes be of critical importance, for example to assess the likelihood of severe adverse effects with NSAIDs, or whether the drug is being used in an age group different to that in which theclinical trials were performed. The co-morbidities of the patient group may be important in determining treatment choice and adverse effects. As an example in the management of hypertension, beta-blockers should be avoided in patients with asthma, and ACE inhibitors preferred in patients with heart failure. Qualitative information such as knowledge, beliefs, and perceptions among patients and their attitudes to drugs will be important in some cases, for example in assessing patient pressures on doctors to prescribe antibiotics, or in designing consumer information/education programs.

1.6.4.4 *Prescriber information*

The prescriber is a critical point in determining drug use. Some sceptics even claim that doctors differ more than patients and that differences in drug prescribing often lack rational explanations. Dissecting the factors that determine prescribing behaviour is therefore often central to understanding how and why drugs are prescribed.

1.6.5 Types of drug utilization study

Drug utilization studies can be targeted towards any of the following links in the drug-use chain:

- The systems and structures surrounding drug use (e.g. how drugs are ordered, delivered and administered in a hospital or health care facility).

- the processes of drug use (e.g. what drugs are used and how they are used and does their use comply with the relevant criteria, guidelines or restrictions); and
- The outcomes of drug use (e.g. efficacy, adverse drug reactions and the use of resources such as drugs, laboratory tests, hospital beds or procedures).

1.6.5.1 *Cross-sectional studies*

Cross-sectional data provide a «snapshot» of drug use at a particular time (e.g. over a year, a month or a day). Such studies might be used for making comparisons with similar data collected over the same period in a different country, health facility or ward, and could be drug-, problem-, indication, prescriber- or patient-based. Alternatively, a cross-sectional study can be carried out before and after an educational or other intervention. Studies can simply measure drug use, or can be criterion-based to assess drug use in relation to guidelines or restrictions.

1.6.5.2 *Longitudinal studies*

Public health authorities are often interested in trends in drug use, and longitudinal data are required for this purpose. Drug-based longitudinal data can be on total drug use as obtained through a claims database, or the data may be based on a statistically valid sample of pharmacies or medical practices. Longitudinal data are often obtained from repeated cross-sectional surveys (e.g. IMS (Intercontinental Medical Statistics) practice-based data are of this type).Data collection is continuous, but the practitioners surveyed, and therefore the patients, are continually changing. Such data give information about overall trends, but not about prescribing trends for individual practitioners or practices.

1.6.5.3 *Continuous longitudinal studies*

In some cases continuous longitudinal data at the individual practitioner and patient level can be obtained. Claims databases are often able to follow individual patients using a unique (but anonymous) identifier. These data can provide information about concordance with treatment based on the period between prescriptions, coprescribing and duration of

treatment. As electronic prescribing becomes more common, databases are being developed to provide Continuous longitudinal data comprising full medical and prescribing information at the individual patient level. Such databases are very powerful, and can address a range of issues including reasons for changes in therapy, adverse effects and health outcomes.

1.6.6 Sources of data on drug utilization

The drug-use chain includes the processes of drug acquisition, storage, distribution, prescribing, patient compliance and the review of outcome of treatment. Each of these events is an important aspect of drug utilization, and most countries have regulations to cover these aspects. Data are collected, or are available, at national, regional and local health facility or household level and may be derived from quantitative or qualitative studies.

Quantitative data may be used to describe the present situation and the trends in drug prescribing and drug use at various levels of the health care system. Quantitative data may be routinely collected data or obtained from surveys.

Qualitative studies assess the appropriateness of drug utilization and generally link prescribing data to reasons (indications) for prescribing. Such studies have been referred to as "dug utilization review" or "dug utilization evaluation"

1.6.6.1 *Large databases*

The increasing interest in efficient use of health care resources has resulted in the establishment of computer databases for studies on drug utilization. Some of the databases can generate statistics for movement at various levels of the drug distribution chain, pharmaceutical and medical billing data or samples of prescriptions. Data may also be obtained from drug importers, wholesalers or local manufacturers. Data from medical practices and health facilities may be used to measure specific aspects of health provision and drug use. Such data may be used to generate indicators that provide information on prescribing habits and aspects of patient care. These indicators can be used to determine where drug use problems exist, provide a mechanism for monitoring and supervision and motivate health care providers to follow established health care standards.

1.6.6.1 *Data from drug regulatory agencies*

Drug regulatory agencies have the legal responsibility of ensuring the availability of safe, efficacious and good-quality drugs in their country. They are thus the repositories of data on which drugs have been registered for use, withdrawn or banned within a country. Regulatory agencies also have inspection and enforcement functions, and are responsible for supervising the importation of drugs and for the issuance of permits for drug registration. It is possible, therefore, to obtain data on the number of drugs registered in a country from such agencies. Where the agency issues import permits and supervise drug importation, data on product type (i.e. generic or branded), volume, and port of origin, country of manufacture, batch number and expiry date may be collected. Where the data reflect total national imports, estimates of quantities of drugs in circulation can be obtained for defined periods and for various therapeutic groups

1.6.6.3 *Supplier (distribution) data*

Data on suppliers may be obtained from drug importers, wholesalers or local manufacturers. In countries where permits or licences are required from drug regulatory authorities and ministries of health before importation of drugs, data may be available from such sources. Data from these sources can generally be used to describe total quantities of specific drugs or drug groups, origins of supplies and type (i.e. branded or generic).

1.6.6.4 *Practice setting data*

Prescription and dispensing data are useful for determining some of the quality indicators of drug use recommended by WHO. These include:

- Average number of drugs per prescription (encounter)
- Percentage of drugs prescribed by generic name
- Percentage of encounters with an antibiotic prescribed
- Percentage of encounters with an injection prescribed
- Percentage of drugs prescribed from essential drugs list or formulary
- Average drug cost per encounter

1.6.7 Over-the-counter and pharmacist-prescribed drugs

Pharmacists and other drug outlet managers may prescribe over-the-counter preparations or pharmacist- prepared drugs that do not require prescription by a physician. Data on such medications may be difficult to obtain especially in environments with weak drug regulation and poor record keeping, but when such information is available from stock or dispensing records, it broadens the understanding of drug utilization patterns.

2. LITERATURE REVIEW.

Nazima *et* al.,[41] conducted a study on Prescribing pattern in a pediatric outpatient department in Gujarat. The aim of the study was to find out the medicine-prescribing pattern in children taking treatment in pediatric out-patient department of a tertiary care teaching hospital in rural Gujarat. Prescriptions were collected randomly. Necessary data were obtained from a total of 606 prescriptions and analyzed for (i) number of medicines per prescription, (ii) medicines prescribed by official names, (iii) essentiality status of medicines, (iv) appropriateness of medicines used and that of prescriptions and (v) cost of prescription. The prescriptions were subjected to measuring the appropriateness of medicines by applying the 'appropriateness scale' to each medicine or medicine combination. The study found that on the basis of appropriateness scale, more than 80% prescriptions could be rated either as appropriate or most appropriate. Only about 1/6 of all prescriptions were found to be inappropriate. Considering the fact that the study was conducted in a tertiary care teaching institution, high proportion of appropriateness is not unexpected. We also found that more than 95% of total cost on account of non-essential medicines was due to prescribing of non-essential fixed-dose drug combinations. If conscious efforts are made to curtail the use of non-essential fixed-dose drug combinations, one can certainly decrease this wasteful expenditure on medicines. The study concluded that for achieving the goal of rational use of medicines it is not sufficient to choose the right medicines only but also they must be employed in the most appropriate manner. There is an ample scope of improving the prescribing pattern by keeping the number of medicines as low as possible, prescribing medicines by official names, using medicines appropriately after selecting and consciously keeping the cost of therapy low.

Rajeshwari *et* al,[42] conducted a Drug Utilisation Study in Geriatric Type 2 Diabetic Patients. This study was aimed- to evaluate the drug utilisation pattern in geriatric T2DM patients. The study was conducted for a period of 6 months (July 2004 to January 2005) in an out-patient department of a tertiary hospital in Mangalore, Kamataka, India. The medical records of 64 geriatric (age >60 years) type 2 diabetic patients attending the diabetic clinic were reviewed. Drug prescribed mainly for DM and hypertension were included along with other drugs used for their comorbidities. Along with drug regimens, demographic data, age, and gender were recorded. The results were analysed using descriptive statistics. In elderly

patients with type 2 diabetes, treatment may be initiated with monotherapy, followed by early intervention with a combination of oral agents, including a sulphonylurea as a foundation insulin secretagogue in addition to a supplemental insulin sensitizer. The study also showed that a combination of sulphonylurea and metformin was most frequently prescribed. Accordingly, metformin is widely regarded as the first drug of choice for most patients with type 2 diabetes mellitus. The study concluded that type 2 diabetic is a progressive and complex disorder that is difficult to treat effectively in the long term. The ^eatment pattern observed in this study corroborates with the accepted pattern of treatment for DM with hypertension, and/or neuropathy. Metformin, glimepiride, and glibenclamide are most commonly prescribed OADs. Enalapril and ramipril among the ACEIs and atenolol and metaprolol among the beta-blockers are the frequently grescribed antihypertensives.

Sipcic *et al.*[43] conducted a study on Drug utilization patterns in Zabljak municipality, Serbia and Montenegro- The aim of the study was to investigate patterns of drug use in the semi-rural municipality of Zabljak, which could be considered a typical municipality in Serbia and Montenegro. The study was conducted from January to March in 2001. There was only one primary care health facility in Zabljak where prescribing was done, and only one state pharmacy, where prescribed drugs were dispensed. During the abovementioned period, the following data were collected from Descriptions and dispensing records: initials, sex and age of the patients, diagnosis, drugs dispensed, and the doses of the drugs. Drug utilization was calculated using the Methodology of the World Health Organization, and expressed in defined daily doses (DDDs) per 1000 inhabitants per day. The diagnoses were classified according to the tenth revision of the International Classification of Diseases. Overall drug utilization in Zabljak was not higher than in other countries, including developed ones. And also the patterns of drug utilization point to certain irrationalities. The study concluded that the total number of drugs utilized per 1000 inhabitants per day was within the acceptable range. However, the pattern of diagnosis did not correspond to the pattern of drug utilisation. There is a need for intervention in order to promote the rational selection and use of drugs among outpatients in Serbia and Montenegro.

Jeschke *et al.*, [44] conducted a study on Evaluation of prescribing patterns in a German network of CAM physicians for the treatment of patients with hypertension. The study was aimed to investigate hypertension treatment strategies among physicians specialized in complementary and alternative medicine (CAM) in Germany by analysing prescribing

patterns and comparing these to the current treatment guidelines issued by the German Hypertension Society. In this prospective, multicentre observational study, which included 25 primary care physicians specialized in CAM treatment, prescriptions and diagnoses were analysed for each consecutive hypertensive patient using routine electronic data. Data analysis was performed using univariate statistical tests (Chi square test, Cochran-Armitage trend test). Multiple logistic regression was used to determine factors associated with antihypertensive medication. Most patients were treated with conventional antihypertensive monotherapies. Beta-blockers were the most commonly prescribed monotherapy, followed by ACE inhibitors. Combination treatment usually consisted of two antihypertensive drugs administered either as separate agents or as a coformulation. The most common combination was a diuretic plus an ACE inhibitor. Patient gender, age, and comorbidities significantly influenced which treatment was prescribed. The study concluded as large majority of antihypertensive treatments prescribed by CAM physicians in the present study complied with the current German Hypertension Society treatment guidelines. Deviations from the guidelines were observed in one of every seven patients receiving some form of CAM treatment.

Chantal *et al*[45] conducted a study on Antihypertensive Drug Therapy in Saskatchewan. The aim of the study was to examine the distribution and determinants of patterns of use of antihypertensive agents in the first 5 years of hypertension treatment in Saskatchewan. Patterns of use and modifications to therapy were derived from a careful examination of medication use in a cohort of 19501 subjects aged 40 to 79 years, without recognized cardiac disease and initiating therapy with an angiotensin -converting enzyme inhibitor, a calcium antagonist, or a b-blocker in Saskatchewan between 1990 and 1993. Angiotensin-eonverting enzyme inhibitors, followed by calcium antagonists and b-blockers, were the most commonly prescribed agents to initiate treatment in our study population. Patients with diabetes were less likely to be dispensed a b-blocker, as were younger and female patients. Previous visits to a cardiologist decreased the likelihood of receiving combination therapy or angiotensin converting enzyme inhibitors but increased that of Using calcium antagonists. Erratic drug-taking behaviors were observed in this Saskatchewan population, hi addition, initial drug use does not seem to be in accordance with the stepped-care approach to hypertension therapy recommended in the Canadian guidelines.

Fowad Khurshid et al.,[46] conducted a study of antihypertensive medication prescribing patterns in a university teaching hospital in south delhi, this study was aimed to investigate the use of antihypertensive drugs in hypertensive patients and to identify whether such pattern of prescription is appropriate in accordance with international guidelines for management of hypertension. This was a prospective analysis. A prescription based survey among patients with established hypertension was conducted at the Medicine Out-Patient Department of University Teaching Hospital in South Delhi, India. Data were collected from patients' medical records as well as patients' interviews. The study concluded that the general pattern of antihypertensive utilization seems to be in accordance with the international guidelines for management of hypertension.

Y.Padmanabha Reddy et a.,l[47] conducted a srudy of drug utilization research is defined as research on "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" and has the principle aim of facilitating the rational use of drugs, our study aims to identify consumption and cost consumption of antihypertensive medications in secondary care hospital. It is a prospective study conducted for the period of 4 months. The required data were collected from the pharmacy from the patient case sheet or through direct patient interview by using suitable patient profile form, and the obtained data were evaluated in relation to the drug use. ATC/DDD method was used to measure the outcome variables. Antihypertensive consumption increased from 10826.8 DDDs in March 2011 to 16437.75 DDDs in June 2011. Overall, the cost consumption has been increased to12523.93 Indian rupees from the initiation of study period to end of the study period. Our study results shows that consumption and cost consumption of antihypertensive drugs were increased during the study period. Increased Drug use and Cost consumption of antihypertensive medications in our study indicates the necessity of preventive care for hypertension and patient has to be provided with knowledge about life style modifications in hypertension to decrease the drug use. This study concluded that Drug utilization research is defined as research on "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" and has the principle aim of facilitating the rational use of drugs, our study aims to identify consumption and cost consumption of antihypertensive medications in secondary care hospital. It is a prospective study conducted for the period of 4 months. The required data were collected from the

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Bajaj et al.,[48] conducted a study of prescription patterns of antihypertensive drugs and adherence to jnc vii guidelines in a tertiary care hospital in north india and drug utilization data of 500 hypertensive patients, attending medicine Out Patient Department of Punjab Institute of Medical Sciences Hospital from October 2010 to March 2011 was collected from 24 hour hospital pharmacy. Following groups of anti hypertensive drugs were analyzed; Angiotensin converting enzyme inhibitors (ACE inhibitors), Angiotensin Receptor Blockers (ARBs), Beta Blockers, Calcium Channel Blockers (CCBs), Diuretics, Alpha Adrenergic Blockers and Central Sympatholytics. Patients suffering from essential hypertension with or without other co-morbid conditions were included in the study. Frequency and proportion of prescribing different groups of anti hypertensive drugs as mon-otherapy or combination therapy and prescription of fixed drug combinations (FDCs) was analyzed. The study concluded that the guidelines given by Joint National Committee on prevalence, de-tection, evaluation and treatment of high blood pressure VIIth re-port suggest that treatment of choice for early stage, uncomplicat-ed, essential hypertension should be thiazide diuretics. Presence of high risk conditions and blood pressure greater than 20/10 mm of Hg above normal is indication for starting therapy with drugs from other classes like ACE inhibitors, ARB's, beta blockers or calcium channel blockers alone or in combination with thiazides. Adherence to treatment guidelines can be monitored by several methods. Drug utilization studies are one such important method. Our data shows that JNC VII guidelines have been followed in totality in this study group. Thiazides are prescribed most frequently alone or in combi-nation with other drugs. ARB's are the most frequently prescribed group in

hypertensive diabetics and asthmatics as angiotensin antagonism is reported to decrease the onset & progress of micro-vascular complications of hypertension and diabetes mellitus [11]. More than half (57.4%) of patients in this study group received two or more antihypertensive drugs.

3. AIM AND OBJECTIVE OF THE STUDY

3.1 AIM

Hypertension is one of the major chronic diseases resulting in high mortality and morbidity in today`s world. A great level of attention is needed in the management of hypertension, because it is one of the major risk factor in the case of cardiovascular disorders. The prescription pattern is an important factor for the effective treatment and control the level of hypertension.

A number of drugs in various combinations are generally used for effective long-term management of hypertension. Drug utilization studies which evaluate, analyse the medical, social and economic outcome of the drug therapy, are more meaningful and observe the prescription attitude of physicians with the aim to provide drugs rationally. The study aimed to assess the antihypertensive utilization pattern in hypertensive patients.

3.2 OBJECTIVE

1. To asses the current practice patterns in pharmacotherapy for hypertension in adult patients.
2. To determine the effect of patients related variable of the treatment.
3. To assess the disease distribution amoung the patients according to gender wise.
4. To assess the use of monotherapy and combination therapy in treatment.

4. METHODOLOGY

This study was conducted at Divine hospital, Salem, Tamil nadu from June 2013 to January 2014. Data was obtained from a prospective series of 310 patients of either sex by scrutinizing the outpatient cards and case sheets of patients attending the clinic. The protocol was prepared as per JNC-VII [11] guidelines.

Inclusion criteria

The data is collected from all the patients of either sex with primary hypertension and the patients without co morbid conditions in medicine outpatient department who are willing to participate in the study.

Exclusion criteria

Patients below the age of 18 years, Female patients who were pregnant, Patients who are not willing to participate in the study, Patients with secondary hypertension, and hypertensive patients with other co morbid conditions were excluded from study.

Study procedure

Data for present study were collected by scrutinizing the patient's case reports, outpatient and inpatient cards. The data collected were analyzed for prescribing patterns of antihypertensive drugs and demographic profiles of the patients suffering from hypertension.

Materials Required

Patient data collection form

Patient`s prescription

Data collection parameters

Patient demographic data

Past medical history

Habits

Physical examination findings

Treatment given.

Method

Information on patients were collected and recorded in standard proforma by reviewing the patient. The demographic details were collected from prescription. Diagnostic details and treatment were also recorded in the patient data entry form.

Factors evaluated were:

Patients characterstics: age,gender and demographic details.

Co morbidities of patients

Treatment.

5. RESULTS

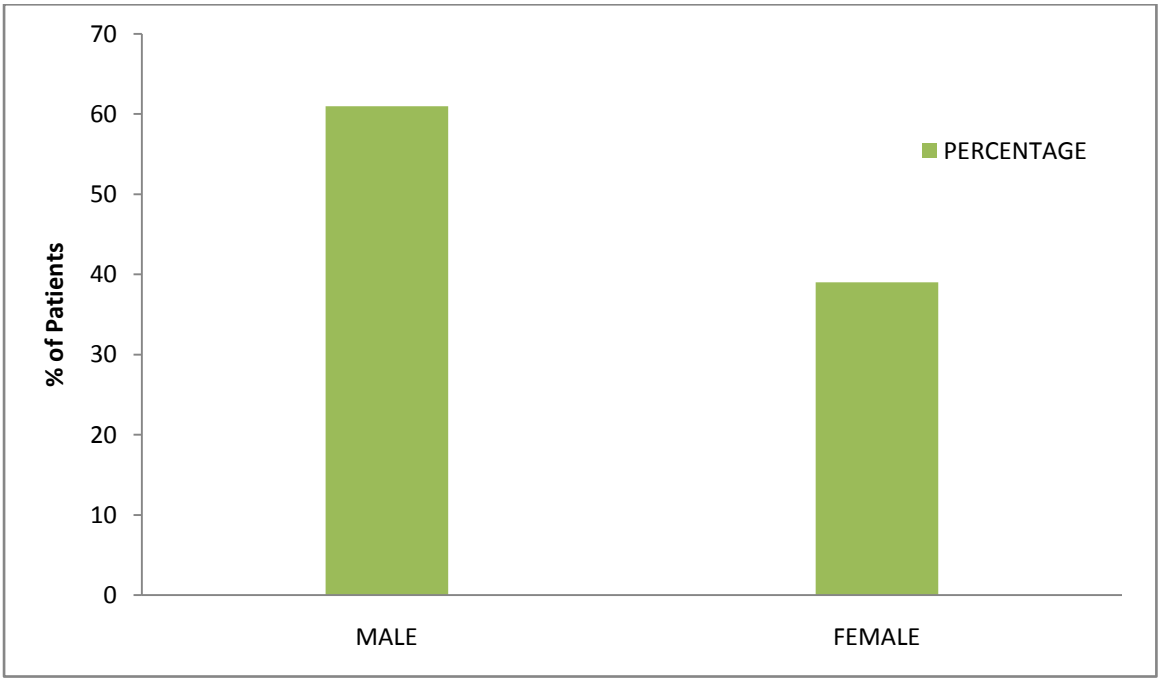
1. Gender wise distribution

Figure 1 shows the gender wise distribution of the patients included in the study. The results revealed that out of 310 patients included the present study, 188 (60.64%) patients were male and 122(39.36%) were female.

Table 1. Gender wise distribution of patients.

GENDER	NO OF PATIENTS (n=310)	PERCENTAGE %
Male	188	60.96
Female	122	39.03

Figure 1. Gender wise distribution of patients

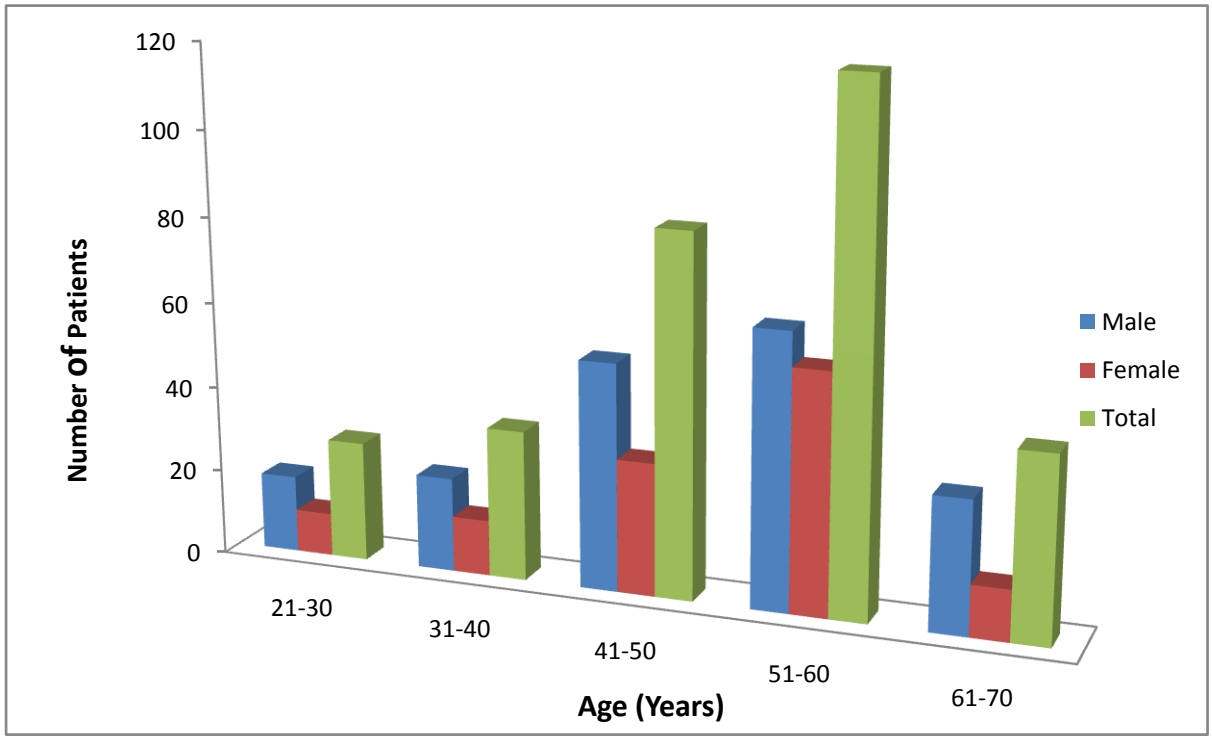


The maximum number of patients were in the age group of 51-60(38,71%) years, followed by age group 41-50(27.09%) years and 13.87% of patients in the age group of 61-70 years.

Table 2. Age and Gender wise distribution of patients

AGE (Years)	MALE		FEMALE		TOTAL (n=310)	
	Number	%	Number	%	Number	%
21-30	18	5.86	10	3.22	28	9.03
31-40	22	7.09	13	4.19	35	11.29
41-50	53	17.09	31	10.00	84	22.09
51-60	64	20.64	56	18.06	120	38.71
61-70	31	10.00	12	3.87	43	13.87

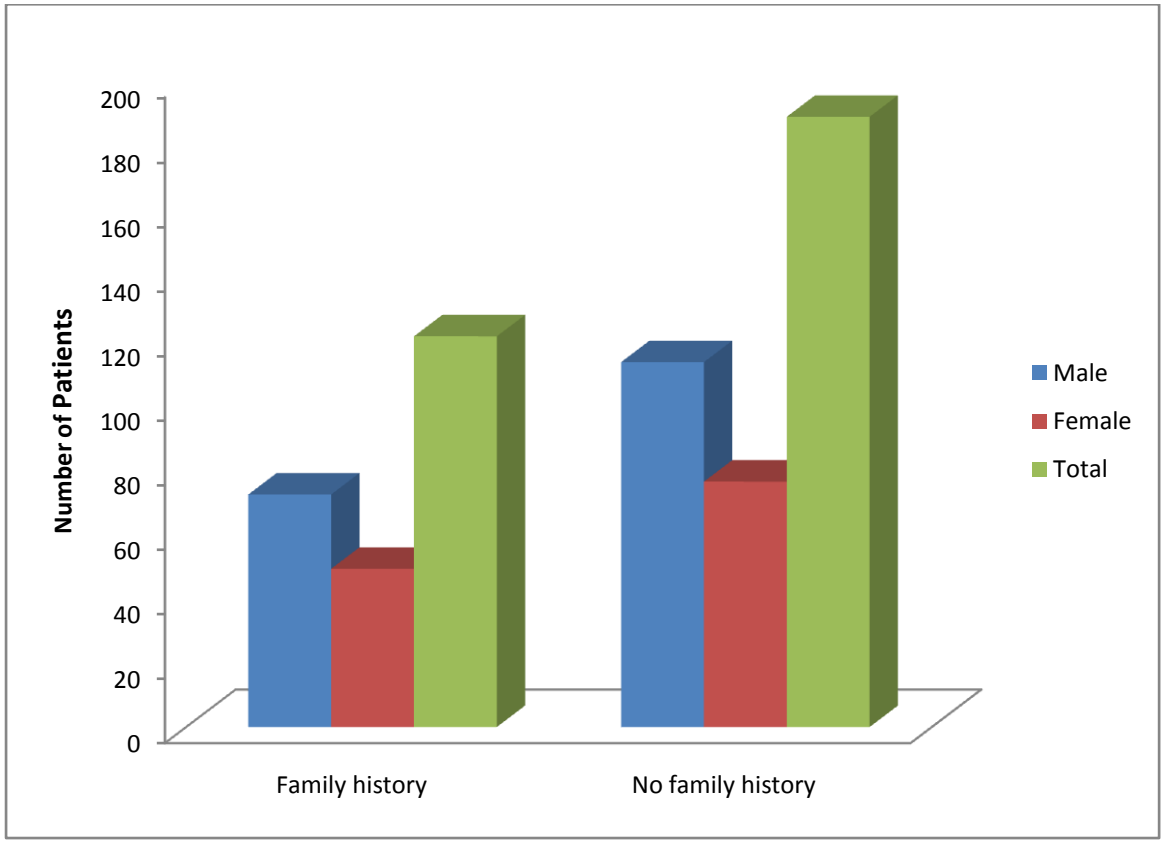
Figure 2.Age and Gender wise distribution of patients.



3. Family history:

Family history of the patients included in the present study is shown in Figure 2.It was observed that 121 (39.03%) patients had a family history of hypertension. Remaining of 189(60.96%) having no family history of hypertension.

Figure 3. Family history of patients



4. Treatment

In the present study drug prescription patterns were classified as single drug, dual drug and triple drug therapy.

The results revealed that, maximum number of patients 181(58.38%) underwent dual therapy followed by 95 (30.64%) underwent monotherapy and 34 (10.96%) were found to take triple drugs. It was also observed that in dual therapy and multiple therapy, most of the prescribed drugs are fixed dose combinations. The higher choice of fixed dose combination products offer a potential means of reducing pill burden and cost for the patient convenience and compliance.

4.1 Single drug therapy

The results revealed that, out of 310 patients who underwent antihypertensive therapy, 95(30.64%) patients were found to be monotherapy. Table 3 & 3.1 shows the drug prescription pattern of mono therapy. In monotherapy, among 95 patients, 24 (25.26%) patients were found to be treated with CCBs, followed by 41 patients (43.15%) were treated with ARBs, 7 (7.36%) patients with ACE inhibitors, 8 (8.42%) of patients with beta blockers and 15 (15.79%) patients with diuretics. The study showed the higher usage of ARBs as single drug in monotherapy followed by CCBs and Diuretics.

Table 3. Single Drug prescribed for the patients.

	Male		Female		Total (n=310)	
Drug type	**Number**	**%**	**Number**	**%**	**Number**	**%**
ACEI*	4	1.29	3	0.97	7	2.26
ARB**	21	6.77	20	6.45	41	13.23
CCB#	14	4.52	10	3.23	24	7.74
DIR##	8	2.58	7	2.26	15	4.84
BB$	4	1.29	4	1.29	8	2.58

*-Angiotensin Converting Enzyme Inhibitor
**-Angiotensin Receptor Blocker
#-Calcium Channel Blocker
##-Diruretics
$-BetaBlockers

Further Sub-classify the mono drug therapy according to types of drug prescribed, the table3.1 expresst the higher usage of Telmisartan 21(6.77%) followed by Amlodipine 15(4.84%) and the Least usage is Enlarpil,carvidelol,atenlol and diltiazem each 2 (0.65%).

Table 3.1. Drug wise single Drug prescribed for the patients.

Drug		Male		Female		Total (n=310)	
		Number	%	Number	%	Number	%
DIR	Hcl*	4	1.29	3	0.97	7	2.26
	Torsimide	4	1.29	4	1.29	8	2.58
ACEI	Enlarpril	1	0.32	1	0.32	2	0.65
	Ramipril	3	0.97	2	0.65	5	1.61
ARB	Losartan	5	1.61	4	1.29	9	2.90
	Olmisartan	5	1.61	3	0.97	8	2.58
	Telmisartan	11	3.55	10	3.23	21	6.77
BB	Atenlol	1	0.32	1	0.32	2	0.65
	Metaprolol	2	0.65	2	0.65	4	1.29
	Carvidelol	2	0.65		0.00	2	0.65
CCB	Amlodipine	9	2.90	6	1.94	15	4.84
	Diltiazem	5	1.61	4	1.29	9	2.90

***-Hydrochlorthiazide**

Figure 4. Pharmacological category of drugs prescribed in monotherapy.

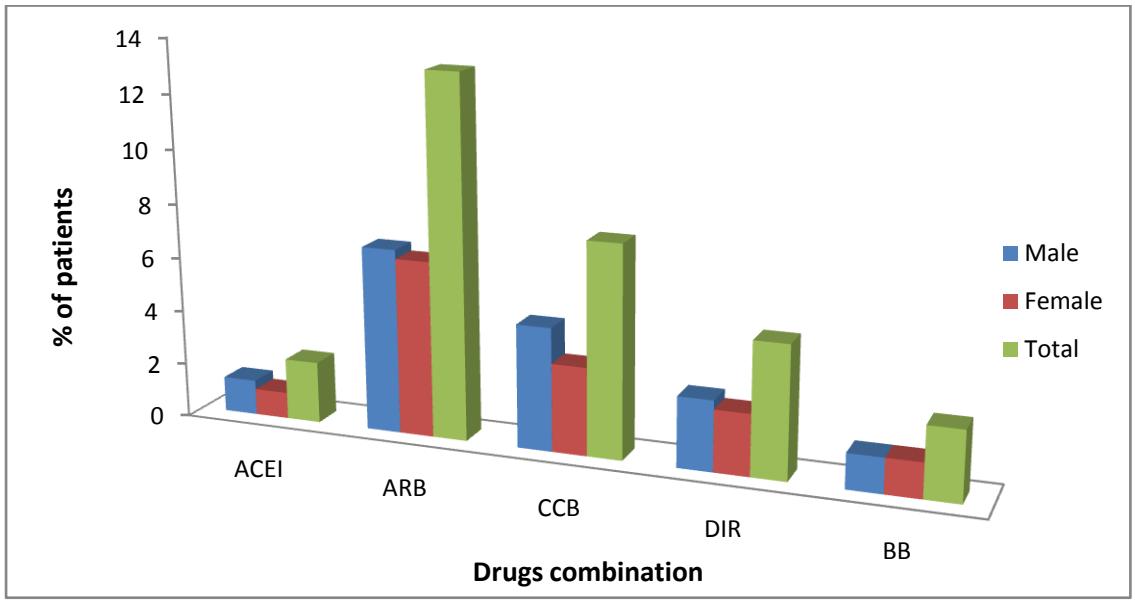
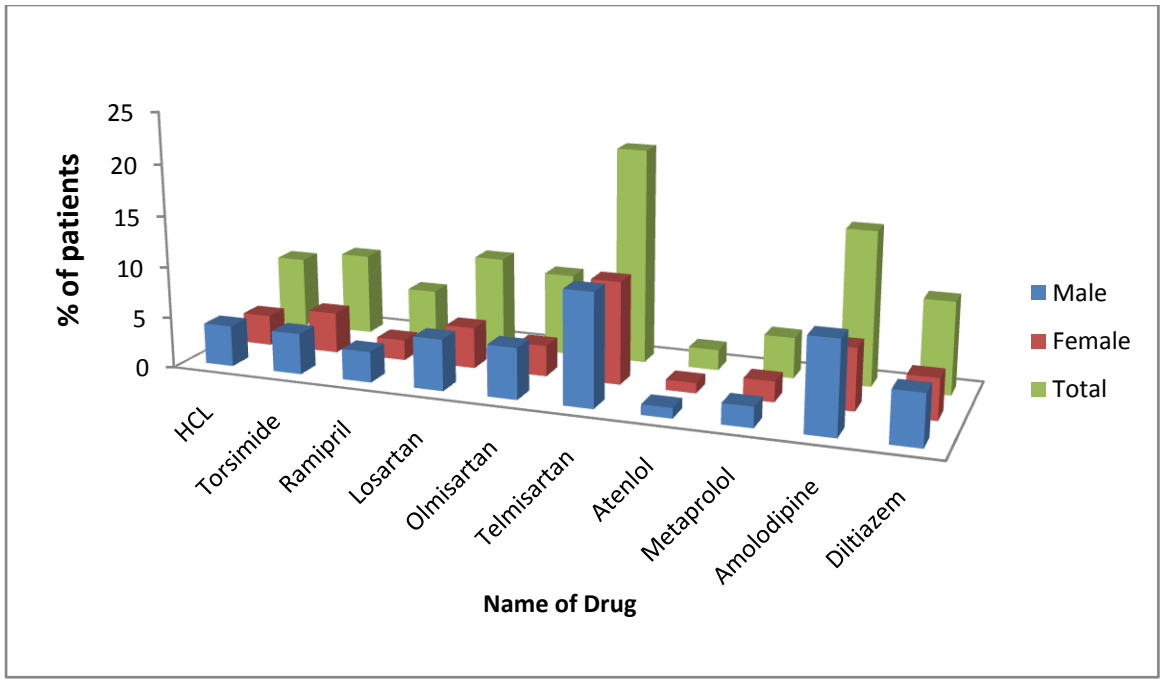


Figure 4.1 Prescription pattern of drugs in Single drug therapy.



4.2 Dual drug therapy

The graph 4.1 shows the prescription pattern of dual drug therapy. Out of 310 patients, for 181 (58,38%) patients ARB+DIR combinations were prescribed followed by ARB+CCB combinations in 53(29.28%) patients and ACE+DIR combinations in 21 (11.60%) patients. In dual drug therapy the most used combinations are Telmisartan with Hydrochlorothiazide, Telmisartan with Amlodipine and Ramipril with Hydrochlorthiazide.

Table 4. Dual Drug prescribed for the patients.

Drug	Male		Female		Total (n=310)	
	Number	%	Number	%	Number	%
BB+DIR	5	1.61	3	0.97	8	1.93
ACEI+DIR	11	3.55	10	3.23	21	4.59
ARB+DIR	40	12.90	32	10.32	72	16.23
ARB+CCB	33	10.65	20	6.45	53	12.73
ACEI+CCB	10	3.23	8	2.58	18	4.06
BB+CCB	5	1.61	4	1.29	9	2.03

Table 4.1 Drug wise Prescription for Dual Drug Therapy for the patients

Drug Type		Male	Female	Total(n=310)
BB+DIR	**Metaprolol+Hcl**	5	3	8
ACEI+DIR	**Ramipril+Hcl**	11	10	21
ARB+DIR	**Telmisartan+Hcl**	21	19	40
	Olmisartan+Hcl	11	9	20
	Losaratan+Hcl	8	4	12
ARB+CCB	**Telmisartan+Amlodipine**	23	12	35
	Olmisartan+Amlodipine	10	8	18
ACEI+CCB	**Ramipril+Amlodipine**	10	8	18
BB+CCB	**Metaprolol+Amlodipine**	5	4	9

Figure 5. Pharmacological category of drugs prescribed in dual drug therapy.

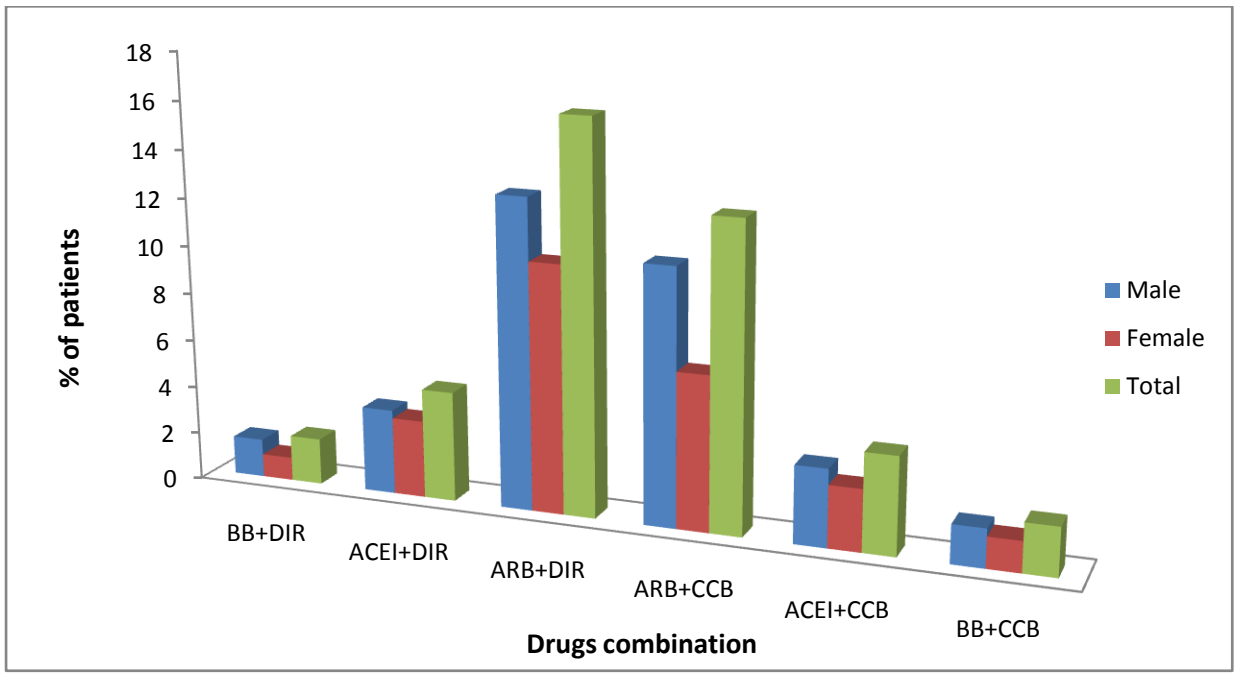
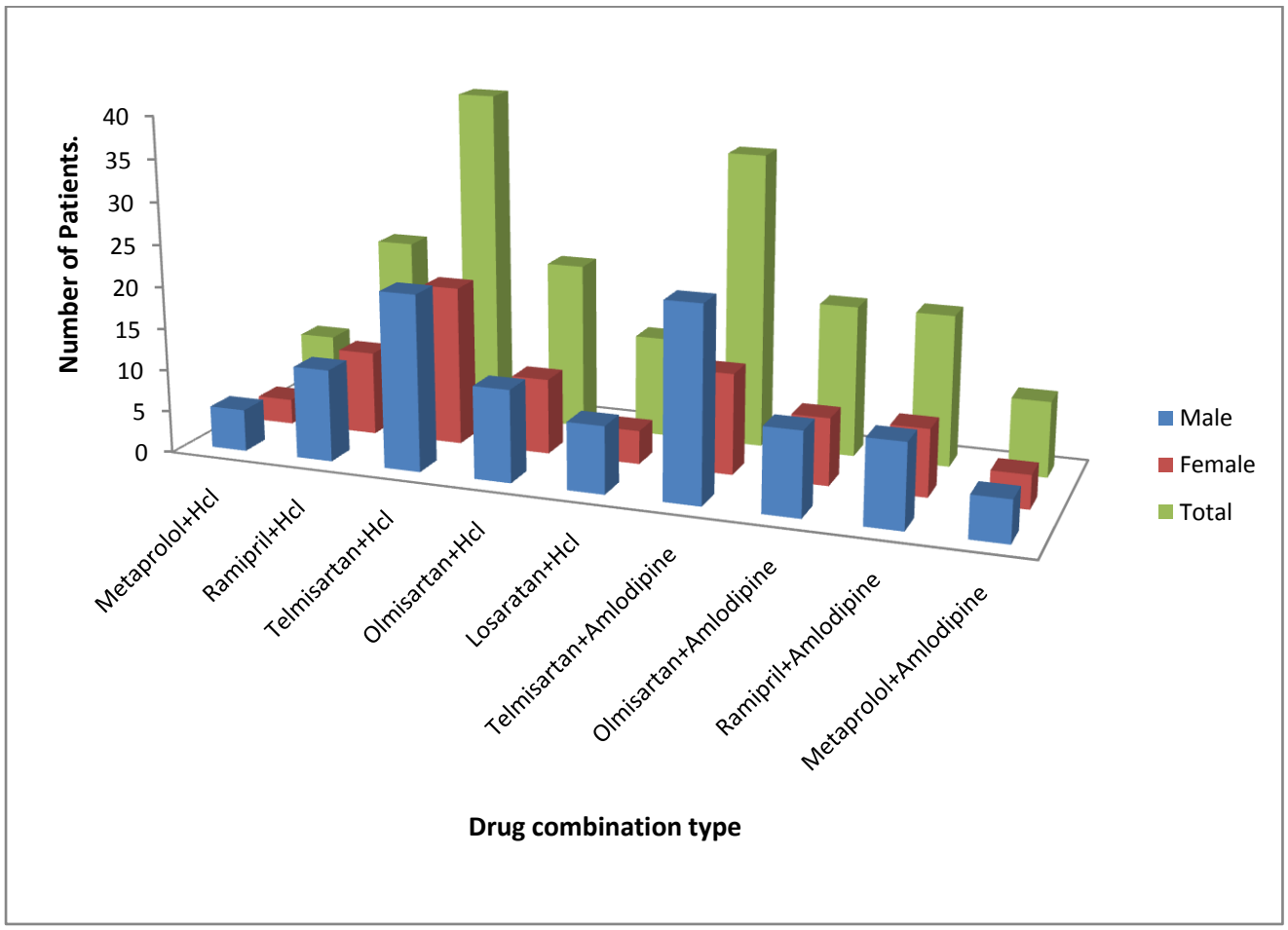


Figure 5.1 Drug wise Double Drug prescribed for the patients

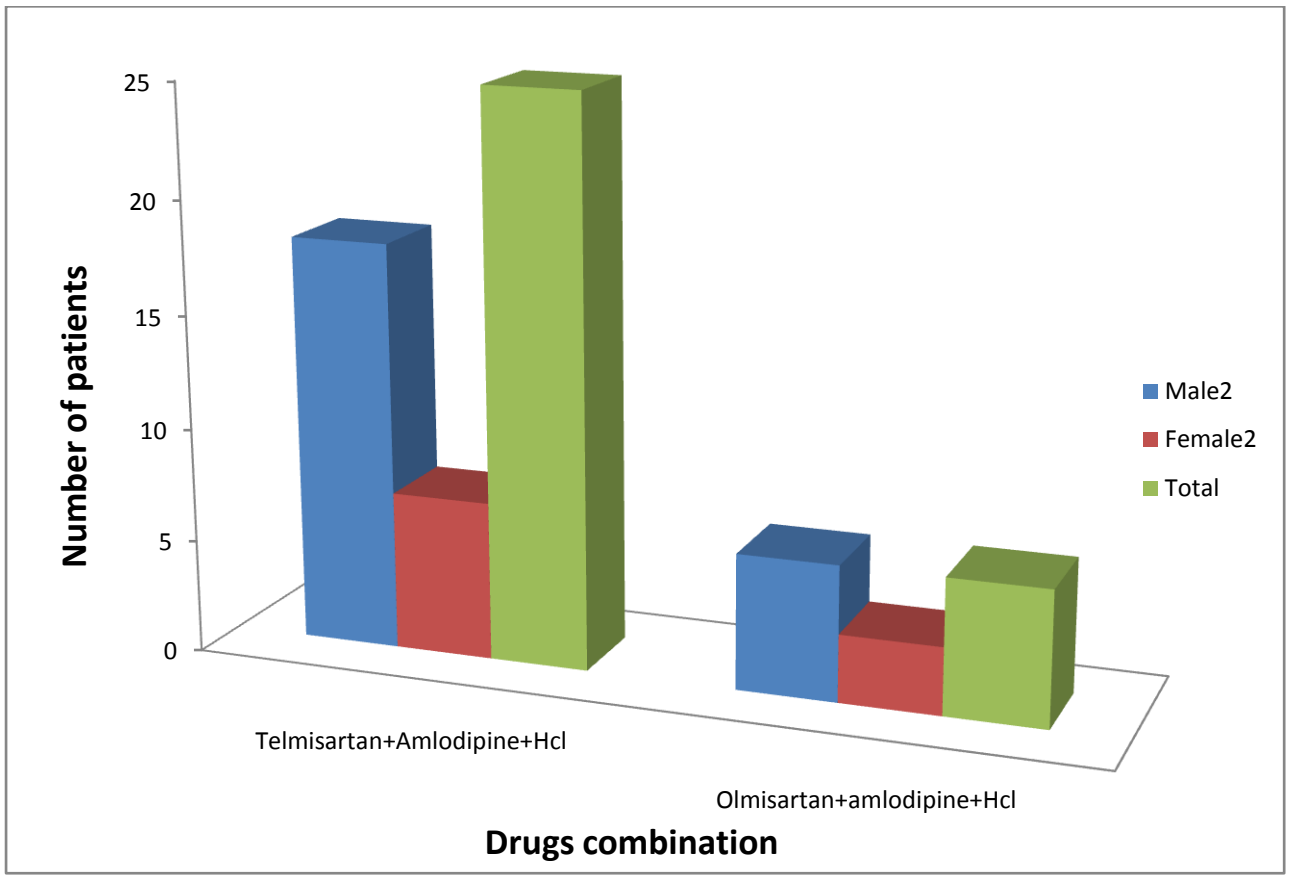


4.3. Triple drug therapy

Table.5. Triple Drug prescribed for the patients.

Drugs		Male		Female		Total (n=310)	
		Number	%	Number	%	Number	%
ARB+ CCB+ DIR	Telmisartan+Amlodipine+Hcl	18	5.80	7	2.25	25	8.06
	Olmisartan+amlodipine+Hcl	6	1.95	3	0.96	6	1.95

Figure 6. Triple Drug prescribed for the patients.



6. DISCUSSION

The aim of the work was to study the prescription pattern of antihypertensive agents in hypertensive patients. A total of 310 patients were included in this study. All are different age group and having hypertension. Drug utilization studies are powerful exploratory tools to ascertain the role of drugs in society. They create a sound sociomedical and health economic basis for health care decision making. It is one of the most effective methods to assess the prescribing pattern of physicians.

AGE WISE DISRTRIBUTION

120(38.71%) patients were fall in the age group of 51-60 years followed 84(22.09%) patients were in the age group of 41-50 years. 28(9.03%) patients in the age group of 21-30 years.

FAMILY HISTORY

In this study 30.96% of patients having family history of hypertension and rest of 69.04% having no family history of hypertension.

TREATMENT

The study observed that the patients were received different type of antihypertensive agents depends upon their blood pressure level. Most frequently used antihypertensive are Angiotensin receptor blocker (13.23%), calcium channel blockers (7.74%), angiotensin converting enzyme inhibitors (2.26%), beta blockers (2.58%) and diuretics (4.54%).

Totally single drug received patients are 30.64%, two drug received patients are 58.38% and triple drug received patients are 10.96%. In the study observed that there are 5

classes of two drug combination therapy were prescribed for some patients to control their blood pressure. And one type of triple drug combination were prescribed for some patients.

Telmisartan is mostly prescribed for controlling and maintaining blood pressure for the patients who suffered from hypertension. The present study also revealed that ARBs are mostly prescribed for the hypertensive patients in all age group in mono therapy and in over all utilization, followed by CCB especially telmisartan and amlodipine. Diuretics are generally recommended as the first line therapy for the hypertension (JNC V, JNC VI)[49]. Combination therapies were more when compared with mono therapy.

The high prescription rate of combination therapy may be due to high prevalence of patients with severe and moderate hypertension. Furthermore, the antihypertensive drug combination therapy should be able to minimize or counteract reflex compensatory mechanisms that often limit the fail in blood pressure. In the present study two drug combinations (58.38%) mostly prescribed followed by mono therapy (30.64%). In the combination therapy Telmisartan with other anti hypertensives are high in usage to control the hypertension. Followed by olmisartan with hydrochlorthiazide and amlodipinie combinations. Utilization of calcium channel blocker in the present study is 7.74% with mono therapy, and overall utilization was (23.34%). According to this study combination therapy is used more than monotheapy and showing the trend changing monotherapy to combination therapy.

The choice of diuretics as the first line antihypertensive drug is consistent with JNC VII guidelines. Diuretics were one of the least prescribed drugs in our study which contradicts the standard guidelines for the treatment of hypertension. This could be due to its effect on the glucose homeostasis and lipid profile as most of our patients were in the elderly

age group. This study was conducted in small group of patients so more studies are recommended to have a better picture of the drug utilization pattern in the country in a large group of patients. This would improve the treatment strategies in the management of hypertension and also help in the effective use of the health care budget.

7. CONCLUSION

Aim of the study was to evaluate the utilization of antihypertensive drugs in hypertensive patients. The study conclude that,

1. ARBs are the most used antihypertensive agent especially Telmisartan..
2. ACEIs are the least prescribed antihypertensive agent.
3. Double and triple combination therapies are more used when compared to monotherepy.
4. In combination therapy ARB and Diuretics (16.23%) are placing the first place in prescription and followed by ARB and CCB (12.73%). The least combination was BB with Diuretics (1.93%).

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