

Evaluation and Study of Various Combinations of Antihypertensive Medications Commonly Prescribed for Outpatient and In-Patient Management of Hypertension in Patients at Tertiary Care Hospital

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Abstract: The purpose of the descriptive drug utilization study was to determine the prescribing patterns of antihypertensive drugs among hypertensive patients attending a tertiary care hospital. The study was conducted over a period of 6 months and analyzed 297 randomly selected prescriptions. The data collected included patient socio-demographic characteristics and the types of antihypertensive drugs prescribed. The results showed that ACE inhibitors and Calcium Channel Blockers were the most commonly prescribed drugs (33.8% and 30.7% respectively) followed by beta-blockers, Angiotensin Receptor Blockers, and diuretics. 55.29% of patients received combination therapy, with the most frequent combination consisting of CCBs and ACE inhibitors. An additional observational and cross-sectional study was carried out over a 1-year period to assess the adherence to joint national committee (JNC-8) hypertension treatment recommendations. The study analyzed 500 prescriptions prescribed for the diagnosis of hypertension. The results showed that 59.8% of the patients were male and 40.2% were female. The JNC 7 guidelines and South African hypertension guidelines were simplified and reduced to four categories for BP measurement. The guidelines emphasized that BP should be recorded with an approved device after the patient has been seated for at least 5 minutes. The study highlights the importance of patient adherence in the successful treatment and outcome of chronic diseases such as hypertension. The findings also show that aggressive blood pressure control is essential to reducing morbidity and mortality. The adherence to JNC-8 treatment recommendations among hypertensive patients attending a tertiary care hospital is a critical aspect of the effective treatment of hypertension.

Keywords: Antihypertensive, Pharmacoepidemiology, Antihypertensive drug utilization, Prescription pattern study

1. Introduction

Chronic kidney disease occurs when one suffers from gradual and usually permanent loss of kidney function over time. This happens gradually, usually over months to years. The term "renal" refers to the kidney, so another name for kidney failure is "renal failure. Mild kidney disease is often called renal insufficiency. Chronic kidney disease (CKD) is defined as persistent kidney damage accompanied by a reduction in the glomerular filtration rate (GFR) and the presence of albuminuria. HTN has been reported to occur in 85% to 95% of patients with CKD (stages 3-5). A cross-sectional study was conducted on hypertensive who visited the General Medicine department in a tertiary care teaching hospital, during the period of August 2013 to August 2014. 1407 new prescriptions were analyzed according to IP/OP numbers of rational drug utilization by using the WHO Core drug use indicator and WHO ATC/DDD metric systems.

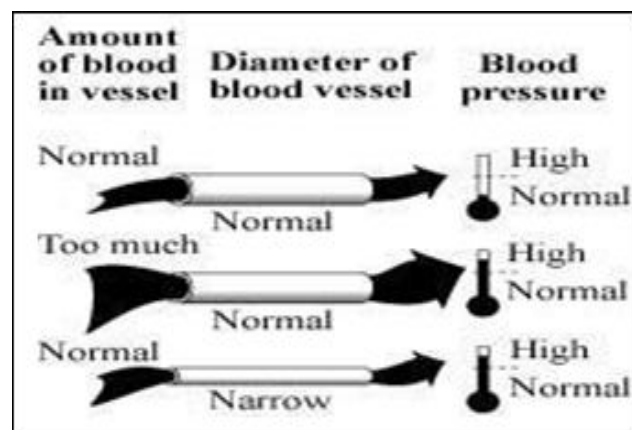


Figure 1: Hypertension Can Result from too Much Fluid in Normal Blood Vessels or From Normal Fluid in Narrow, STIFF, ORCLOGGED BLOOD VESSELS

The World Health Organization (WHO) 2013 has estimated that high blood pressure (BP) is a major public health issue and causes one in every eight deaths, with hypertension being the third leading silent killer in the world. Hypertension accounts for 9.4 million deaths worldwide every year. Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke (World Health Organization (WHO), 2013). In India, the situation is more alarming as hypertension attributes to nearly 10% of all deaths. The prevalence of hypertension in India is reported to vary from 10 to 30.9%. The average

prevalence of hypertension in India is 25% in urban and 10% in rural inhabitants. Cardiovascular diseases are projected to cause 4.6 million deaths in India by 2020 (Mahmood et al., 2011). It is estimated that the worldwide prevalence of hypertension would increase from 26.4% in 2000 to 29.2% in 2025. Anti-hypertensive pharmacotherapy effectively reduces hypertension-related morbidity and mortality (Rachana et al., 2014).

Drug utilization studies, which evaluate and analyze (Fowad et al., 2012) the medical, social, and economic outcomes of drug therapy are more meaningful and observe the prescribing attitude of physicians with the aim to provide drugs rationally. Drug utilization research is an essential part of Pharmacoepidemiology as it describes the extent, nature, and determinants of drug exposure (Ushadevi et al., 2013).

The DDD metric along with the ATC classification form a powerful technical tool used for analyzing patterns of drug utilization and the quality of drug use and health outcomes and also for measuring the number of defined daily doses per thousand patient days (DDD/1000 patient days) and 100 patient days (DDD/100 patient days). The advantages of the

DDD methodology are that it can measure drug exposure, is inexpensive, easy to use, and allows integration with other databases (WHO, 2010).

The present study aims to evaluate on drug utilization pattern of anti-hypertensive medications therapy using WHO-recommended core drug use indicators like (a) Prescribing indicators; (b) Patient care indicators and (c) Facility indicators. Also to evaluate the total consumption or utilization of antihypertensive drugs in hypertensive subjects using the ATC/DDD metric system at the general medicine ward in a tertiary care teaching hospital.

Measurement of drug utilization of anti-hypertensive medication using the ATC/DDD metric system:

Measurement of drug utilization of antihypertensive medications was observed as follows: Angiotensin-converting enzyme inhibitor (ACE-I) Enalapril and Ramipril; beta blocking agents–metoprolol, atenolol, propranolol, nebivolol; calcium channel blockers–

Generic name available in study site/Class

Angiotensin converting	Enzyme inhibitor (ACEI)					
	Aug'2013	Sep' 2013	Oct'2013	Nov'2013	Dec'2013	Jan'2014
Ramipril	3.6	20	35	4.05	4	31
Enalapril	29.25	16.25	16.25	15.5	14.75	26.25
Beta blocking agents						
Metoprolol	4.61	4.55	0.75	0.25	3.58	20.13
Atenolol	1.5	3.2	3.5	2.0	1.5	2.9
Nebivolol	6.7	25.0	12.0	8.0	10.0	5.0
Propranolol	0.8	0.75	0.25	1.0	1.2	0.3
Calcium channel blockers (CCBs)						
Verapamil	1.5	2.2	1.3	1.1	1.9	2.2
Amlodipine	25.5	85.5	8.5	2.0	19.0	41.0
Angiotensin-converting II inhibitor						
Telmisartan	8.0	2.0	2.0	3.0	4.3	1.9
Diuretics						
Furosemide	28.5	33.0	3.5	6.0	1.5	38.75
Hydrochlorothiazide	1.1	1.2	1.1	0.4	1.0	2.2

Verapamil and amlodipine; angiotensin converting II enzyme inhibitor-telmisartan and diuretics. Furosemide and hydrochlorothiazide drugs were used during this period (August, 2013 to August, 2014) and monthly consumption of antihypertensive drugs was calculated in defined daily dose study data shown in Tables 8 to 10. During this study period (August, 2013 to August, 2014) the anti-hypertensive drug consumption data were collected and analyzed in general medicine ward. Total 82 subjects were randomly collected and enrolled in the study. Twenty eight (28) subjects were admitted in MIMCU and FIMCU, and 54 subjects were admitted in CCU. The number of beds available in the ward is 450 and the number of days spent was 397 days. The average bed occupancy rate during this study period was 0.6. Amlodipine medication was most frequently utilized with respect to the number of 32.55 DDD/100 bed days and then followed by Ramipril, with 24.70 DDD/100 bed days and enalapril, with 19.55 DDD/100 bed days. The total consumption of anti-hypertensive drug was detected to be 122.07 DDD/100 bed-days. The impressed number of DDD assigned for each anti-hypertensive is given by the DDD/ATC WHO metric system as recorded in based

evaluation study and the study is used as one of the systematic way for rationality and assessment of drug utilization, aiming to measure the rationality which can reduce morbidity and mortality. Multiple guidelines discuss the importance of lowering blood pressure (BP) to slow the progression of renal disease and reduce cardiovascular morbidity and mortality⁴⁻⁶. However, in order to achieve and maintain adequate BP control, most patients with CKD require combinations of anti-hypertensive agents; often, up to three or four medication classes may need to be employed⁷.

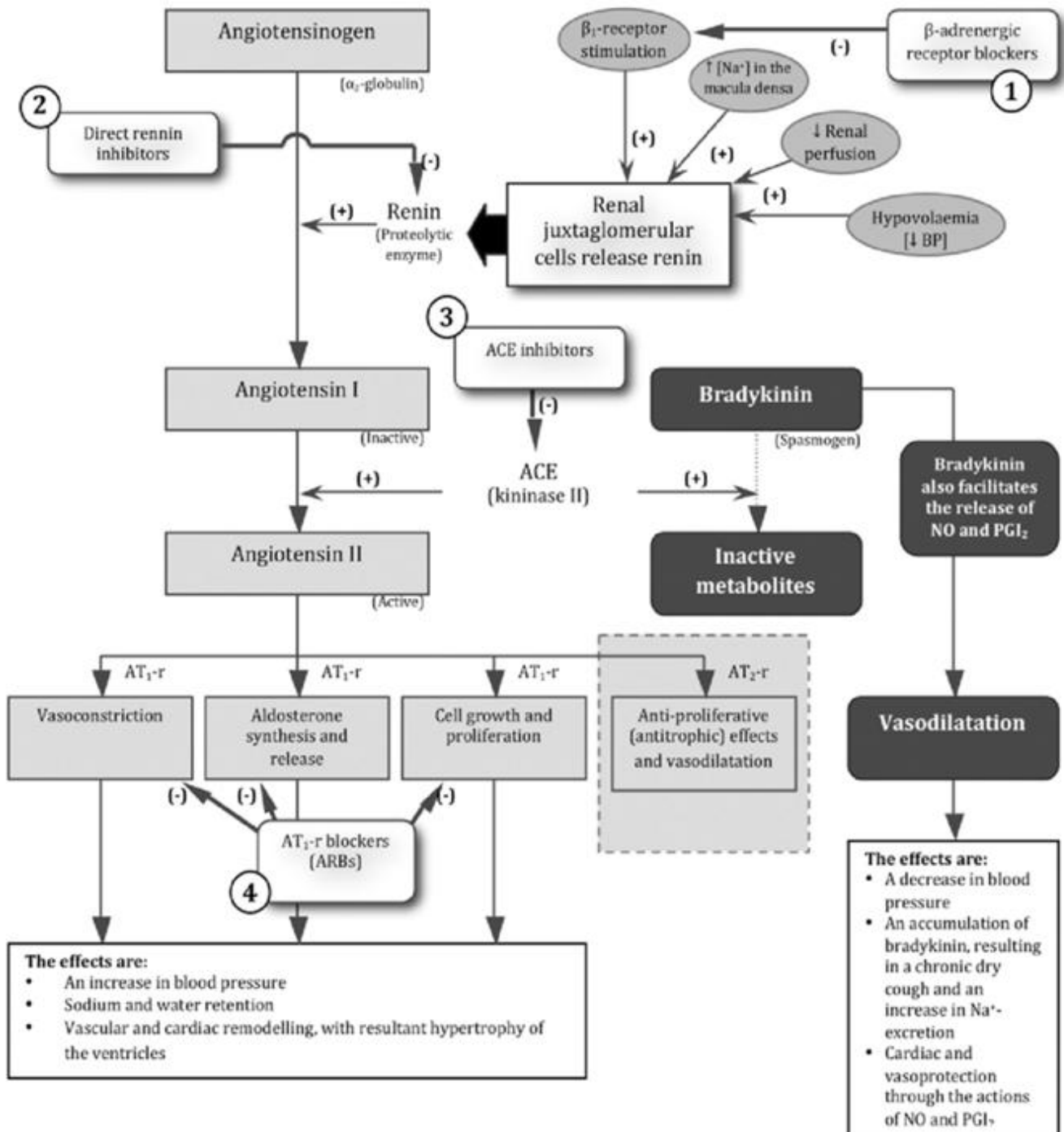
Goals of Therapy:

Patients with non-diabetic and diabetic CKD should have a target BP goal of <130/80 mm Hg. Ultimately, the rationale for lowering BP in all CKD patients is to reduce renal and cardiovascular morbidity and mortality. Maintaining BP control and minimizing proteinuria in patients with CKD and HTN is essential for the prevention of the progression of kidney disease and the development or worsening of CVD.

Recent literature suggests that BP targets in diabetic and non-diabetic CKD may need to be individualized based on

proteinuria. Some trials have failed to show a reduction in cardiovascular or renal outcomes in diabetic and non diabetic patients with CKD when a BP target of <130/80mmHg is achieved compared to lowering BP to <140/90 mm Hg. However, patients who have proteinuria are less likely to experience a decline in renal function,

kidney failure, or death when the lower BP target is achieved. Future guidelines may likely include a lower BP goal, <130/80mmHg, for patients with proteinuria but maintain a goal of <140/90mmHg for patients without proteinuria.



Rational Drug Use:

Irrational use of Medicines is a global phenomenon. Rational use of drugs may be defined as: Patients receive medications appropriate to their clinical needs, in doses that meet their requirements, for an adequate period of time, and at the lowest cost to them and their community. Over use, poly pharmacy, and incorrect use of drugs are the most common drug use problems today.

Irrational use of drugs may result due to various reasons, including prescribing errors and over-the-counter drugs.

Irrational use of medicines may lead to serious negative health and economic consequences. Many irrational drug combinations are available in the Indian market. Proper implementation of rational drugs will improve the quality of life and result in better community healthcare

Treatment:

According to the updated 2014 Eighth Joint National Committee (JNC-8) guidelines on HTN, evidence from clinical trials indicates that antihypertensive medications (blood pressure medication) should be initiated in patients

less than 60 years old if the systolic blood pressure is persistent >140 mmHg and the diastolic blood pressure is persistent >90 mm Hg despite non-pharmacologic therapy. If a patient is 60 years old and older, antihypertensive therapy should be initiated if the systolic blood pressure is >150mmHg and the diastolic blood pressure is >90mmHG.

All hypertensive patients should be counseled on the appropriate lifestyle modifications needed to help lower blood pressure. Evidence has shown that societies with an average sodium intake (more than 2.3 grams per day) have a greater number of patients diagnosed with HTN. High amounts of sodium intake lead to increased volume in the blood stream. This places increased pressure on the heart to pump blood throughout the body. As a result, blood pressure can become elevated¹³⁻¹⁵. The American Heart Association (AHA) recommends limiting sodium intake to less than 1500 mg per day (1.5 grams). Since most dietary salt is found in packaged and processed foods, limiting their intake and finding healthier alternatives is beneficial for blood pressure reduction.

Restrictive diets, like the Dietary Approaches to Stop Hypertension (DASH) diet, have been found to help lower blood pressure. The DASH diet emphasizes a food plan high in fruits, vegetables, whole grains, poultry, and fish while limiting sweets, sugar-sweetened beverages, and red meat. Furthermore, the DASH diet recommends that men restrict alcohol intake to two or fewer drinks a day and women to one or less. This recommendation is based on evidence indicating that patients who excessively drink alcohol have had a higher incidence of high blood pressure than those who drink alcohol in moderation. In addition to dietary modifications, exercise is recommended.

Both aerobic exercise and resistance training have been shown to lower blood pressure and improve overall cardiovascular health. Examples of aerobic exercise include walking, jogging, swimming, and biking. The AHA recommends an average of 40 minutes of moderate to vigorous-intensity aerobic exercise three to four times a week to help lower blood pressure.

Pharmacological therapy is initiated if non pharmacologic treatment is ineffective in managing high blood pressure. Initial pharmacological therapy for HTN includes thiazide diuretics, long-acting calcium channel blockers (CCB), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs). Blood pressure goals for HTN are specific to a patient's age and comorbid diseases. It is important to note that these goals are updated from those previously recommended in past guidelines (Seventh Joint National Committee Guidelines). Agents that not only lower BP but also reduce proteinuria are recommended as first-line therapy for most patients with CKD and HTN; data indicate there may be significant long-term benefits in both cardiovascular and renal outcomes when proteinuria is decreased.

Several classes of antihypertensive agents may have a role in the treatment of CKD and HTN. Agents that target the renin-angiotensin aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors or

angiotensin II receptor blockers (ARBs), are generally considered first-line antihypertensive therapy for this patient population. The following are the various antihypertensive drugs.

ACE-Is and ARBs: ACE-Is block the conversion of angiotensin I to angiotensin II and the degradation of bradykinin. It seems likely that the accumulation of bradykinin leads to persistent dry cough, a recognized side effect that occurs in 5 to 20% of patients on ACE-Is. Angioneurotic edema can occur with ACE-Is and ARBs, although the relative frequencies and mechanisms are unclear. ARBs act by competitively antagonizing the interaction between angiotensin II and angiotensin receptors and were first introduced as an alternative to ACE-Is in patients who had an ACE-I-induced cough.

Drug Combinations: ACE-Is and ARBs are valuable adjuncts to diuretics for treating high BP and vice versa. Co-administration of beta-blockers and calcium channel blockers with ACE-Is or ARBs is also acceptable.

Diuretics: Salt and water retention are major factors contributing to high BP in CKD patients and to morbidity and mortality through systemic or pulmonary edema. Thus, diuretics potentially have an important role in controlling hypertension in this clinical setting.

Drug Combinations: Thiazides are often one of the first 2 or 3 drugs used for BP lowering in CKD, particularly if there is edema or if ACE-Is or ARBs have already been prescribed. Thiazides are known to potentiate the effect of other antihypertensive agents, particularly ACE-Is and ARBs, and may also reduce the risk of hyperkalemia. The inclusion of thiazides in fixed-dose combinations with other antihypertensives is convenient for patients and may improve compliance.

Beta-blockers: All beta-blockers effectively reduce BP; other issues may influence whether they are appropriate in a given patient and which specific drug is chosen since beta-blockers vary widely in their pharmacology.

Drug Combinations: Beta-blockers have often been combined with diuretics; there are no theoretical reasons why beta-blockers should not be combined with ACE-Is or ARBs. The combination of atenolol or bisoprolol (which accumulate in CKD patients) with bradycardia-inducing drugs such as nondihydropyridine calcium-channel blockers is not recommended. The combination of lipophilic beta-blockers (which cross the blood-brain barrier) with other centrally acting drugs such as clonidine may lead to drowsiness or confusion, particularly in the elderly.

Calcium Channel Blockers: The major sub classes are the dihydropyridines (*e.g.*, amlodipine, nifedipine, and lercanidipine), the non-dihydropyridine benzothiazepines (*e.g.*, diltiazem) and the phenylalkylamines (*e.g.*, verapamil). Dihydropyridines tend to be more selective for vascular smooth muscle Vasodilatation with less action on the myocardium.

Accordingly, the side effects may include fluid retention and ankle edema, which can be problematic inpatients with CKD. Dizziness, headache, and redness of the face are also common side effects. Non-dihydropyridines directly affect the myocardium, including the sinoatrial and atrioventricular nodes, and reduce the heart rate and cardiac-muscle contraction.

Drug Combinations: Fluid retention, seen particularly with dihydropyridines, can be problematic in patients with CKD, such that avoiding other vasodilators may be sensible. Combining non-dihydropyridines such as verapamil and diltiazem with beta-blockers can lead to severe bradycardia, particularly in patients with advanced CKD if drugs such as atenolol and bisoprolol, (that accumulate in CKD) are used.

Centrally Acting Alpha-agonists: Centrally acting alpha-agonists cause vasodilatation by reducing sympathetic outflow from the brain. The main agents in use are methyldopa, and clonidine. They are valuable as an adjunct therapy for hypertension in CKD patients.

Drug Combinations: The combination of alpha-agonists with thiazides probably advantageous in reducing vasodilatation-induced fluid retention. Combination with other antihypertensive drugs is usually trouble-free, but caution is advised if the agents have similar side effects.

Alpha-blockers: Alpha-adrenergic blockers selectively act

to reduce BP by causing peripheral vasodilatation. Prazosin, doxazosin, and terazosin are the alpha-blockers most commonly used in treating hypertension. Alpha-blockers are an adjunctive treatment for elevated BP in CKD patients in whom ACE-Is, ARBs, diuretics, calcium-channel blockers, and beta-blockers have failed or are not tolerated. Alpha-blockers are not considered a first-line choice because of the common side effects of postural hypotension, tachycardia, and headache.

Drug Combinations: There is little data about alpha-blocker combinations with other BP-lowering drugs. Vasodilatation can lead to peripheral edema, so diuretics are commonly combined with alpha-blockers, although the efficacy of this maneuver has not been studied. Alternatively, a non-selective beta-blocker can be used.

Direct Vasodilators: Hydralazine and minoxidil act by directly causing vascular smooth-muscle relaxation and Vasodilatation. Its side effects (e.g., severe fluid retention, headache, tachycardia, hirsutism, and pericardial effusion) limit its use to the most resistant cases.

Drug Combinations: Because of the side effects of fluid retention and tachycardia, direct vasodilators (especially minoxidil) are usually combined with a beta-blocker and loop diuretic.

Table 2: Monthly consumption of anti-hypertensive drugs in Defined Daily Dose (DDD) in a Tertiary Care Teaching Hospital (From Feb' 2014–Aug'2014)

Generic/Brand name Feb'	March	April	May	June	July	August
Available in study 2014	2014	2014	2014	2014	2014	2014
Angiotensin converting enzyme inhibitor (ACEI)						
Ramipril	132	50.5	31.4	17	40	2.25
Enalapril	24.25	29.0	20.75	27.25	10.5	22.0
Beta blocking agents						
Prolomet	12.06	2.59	5.4	4.9	1.41	0.68
Atenolol	1.4	2.2	2.1	1.3	1.4	1.1
Nebivolol	7.8	13.5	2.2	6.9	8.9	10.0
Propranolol	0.3	0.6	0.5	0.3	0.2	0.3
Calcium channel blockers (CCBs)						
Verapamil	1.1	1.2	1.8	1.9	1.2	0.8
Amlodipine	51.0	19.0	61.0	76.0	6.0	13.0
Angiotensin converting enzyme II inhibitor						
Telmisartan	1.0	0.6	0.5	1.1	2.1	0.7
Diuretics						
Furosamide	10.0	5.8	1.8	2.9	6.0	10.0
Hydrochlorthiazide	1.1	1.2	1.0	0.5	2.2	1.1

Classification of blood pressure:

According to the JNC 7 guidelines and the South African hypertension guidelines, the seven categories of BP defined in the JNC 6 were simplified and reduced to four. BP should be recorded with an approved device in a patient who has been seated for at least five minutes prior to taking the measurement. The patient should not have smoked, or taken any caffeinated drink or food in the preceding 30 minutes. To document postural hypotension in patients aged 60 years and older, and those with other co-morbid conditions, e.g. diabetes mellitus, BP should also be recorded after the patient has been standing upright for at least one minute.^{15, 18} The cuff size appropriate to the size of the patient's arm is

an important parameter, and both the SBP and DBP should be recorded.

Suspected "white coat" readings (higher readings in the office compared to readings outside), or masked hypertension (normal readings in the office and higher readings outside)

- In patients with co-morbid conditions according to which they are classified as a so-called high risk group, in order to guide antihypertensive medication
- Refractory hypertension
- To improve compliance with treatment (the self-

monitoring of BP only).

Blood Pressure Classification	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
Normal	<120	and <80
Pre- hypertension	120- 139	or 80- 89
Stage I hypertension	140- 159	or 90- 99
Stage II hypertension	>160	or >100

Single therapy (54.17%) Vs Multiple combinations therapy (45.83%)

Mono therapy was more frequently used than combination therapy (54.17% vs. 45.83%) and very least prescribed drugs rate was as follows: Angiotensin II receptor antagonist 32 (1.5%), angiotensin converting enzyme inhibitor (ACEI)+ angiotensin II receptor blockers + β -Blocker 17(0.79%) proposed in this present study. Combination therapy drug utilization had very less usage when compared with the study carried out by Fowad et al.(2008) Monotherapy of angiotensin converting enzyme inhibitor (ACEI) 31.7% and angiotensin converting enzyme inhibitor (ACE I) + β -Blocker 251 (17.8%) were more frequently utilized than reported by Fowad et al. (2008) who revealed that Monotherapy 45.4% vs. Combination therapy 54.6%.

2. Material and Methods

Study Design: The study was observational study.

Source of Data and Materials:

- Patient consent form.
- Patient data collection form.
- Patient case note/prescription.

Inclusion Criteria:

- In patients of department of Nephrology and dialysis unit of SVS Hospital and Medical college.
- Male and female patients with no age restrictions.
- Patients with hypertension as a comorbid condition are included.

Exclusion Criteria:

- Patients who are not willing to give consent.
- Pregnant, Patients with comorbid other than listed in inclusion criteria.

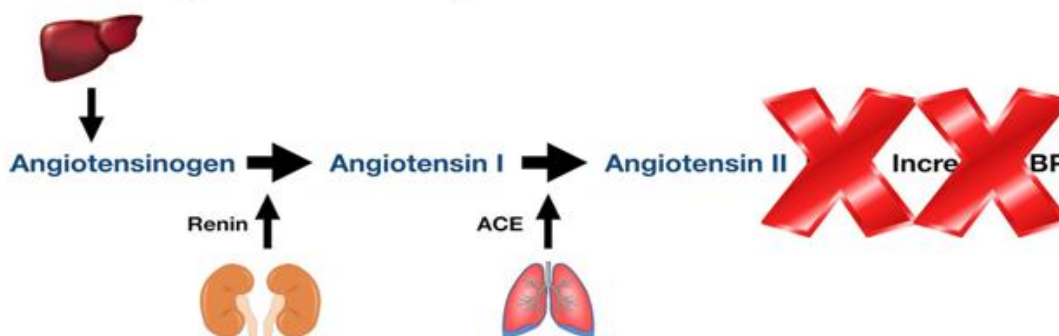
Method of Data Collection:

- Data collection form
- Patient interview

Study Procedure: This is a comparative study where patients eligible are enrolled in the study after obtaining the consent. The data collection form will be prepared and used. This form mainly contains the patient's demographic details and medication chart with diagnosis. Also, the prescription pattern of the patient, daily usage of antihypertensive drugs percentage was calculated.

Antihypertensive Mechanism of Action Angiotensin II Receptor Blockers (ARBs)

Block Angiotensin II Receptors



3. Result and Discussion

The total antihypertensive drug consumption in General medicine wards was measured in impressed number of DDD/100 bed-days. In our study, class wise found that total antihypertensive consumption of (ACE I - Ramipril and Enalapril) (670.55 DDD) was highly utilized. But drug wise, high utilization was found in the general medicine wards having amlodipine with 32.55 DDD/100 bed days than other drugs which we analyzed in present study. A similar study report was found by Joel et al., (2014) (amlodipine 33 DDD/100 bed days) and another study by Jhaveri et al. (2014) postulated that amlodipine utilization in the wards was 29 DDD/100 bed-days. Current study found that total antihypertensive drug consumption in the General medicine

wards were 122.07 DDD/100 bed-days.

4. Conclusion

ACE inhibitors were most frequently utilized and amlodipine was the highest consumed in the internal ward during this study. The clinical pharmacists can be effectively employed for rationality use of medication in hypertensive population on a routine basis. In the present study, cross-sectional, observational study parameters were carried out and evaluated, and measured based on WHO core drug use indicator and ATC/WHO DDD metric system. Here, many of the prescriptions were rational, but further improvement is needed in drug prescribing practices and prescribers may contribute to the progress of rational prescribing drug

practices in hypertensive study population. Patients too need to express their interest to know more about the drugs they have been prescribed, and this can promote a safe knowledge on their illness and special care, which would improve their quality of life. Further, the present study can lead to finding out the influence of prescribing practice on cost of burden in the subjects which will be carried out in a future research.

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