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DRUG UTILISATION EVALUATION OF ANTI HYPERTENSIVE DRUGS IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT: Objective: To assess the drug utilization evaluation of antihypertensive agents in diabetic and non-diabetic patients with chronic kidney disease. **Method:** Retrospective observational study was conducted in inpatient Nephrology department of B.B.R. Hospital from Sep 2016 to Feb 2017 and 155 case records of patients diagnosed with CKD and HTN, above 18 yrs of age, belonging to both genders were collected. Required Information from the patient's case sheets was collected using a well designed data collection form. **Results:** The prevalence of CKD is more in male than in female and most commonly age group of > 60 yr was affected with CKD. Our study showed that majority of patients needed multiple drug therapy to control hypertension. Diuretics were most commonly prescribed drugs. The preferable drugs given among anti-hypertensive were diuretics, calcium channel blockers, beta blockers, alpha blockers, ARB'S. **Conclusion:** Most of the CKD patients were Male (63.87%) in distribution. Of the 155 cases, 69.03% of patients were also suffering from Diabetic. Majority of patients (both diabetic and non-diabetic hypertensive patients with CKD) were prescribed with Diuretics (40.71%), of which Furosemide (31.12%) was predominantly seen. 65% of prescribed drugs were brand name drugs. Polypharmcy was observed in most of the prescriptions.

INTRODUCTION: Chronic kidney disease is characterized by progressive destruction of renal mass with irreversible sclerosis and loss of nephrons over a period of months to years [1]. It is estimated that one out of 10,000 people suffer from CKD in India and around 100 thousand new patients develop ESRD in India annually.

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Approximately 1 of 5 adults with high blood pressure has CKD and medical care for CKD patients is complex, due to widespread co-morbidities and major risk factors for CKD [2].

The most common risk factors and other characteristics among the subjects diagnosed with CKD were hypertension (64.5%), anaemia (40.7%) and diabetes (31.6%) [3]. CKD develops in about third of patients with diabetes, and while in people with treated essential hypertension, CKD is present in a small percentage of patients [4]. Hypertension is the most important modifiable risk factor for coronary heart disease, stroke (the third leading cause of death), congestive heart failure, end-stage

renal disease, and peripheral vascular disease. Hypertension is associated with increased cardiovascular risk [5] and reducing blood pressure with antihypertensive agents significantly decreases that risk; diabetes is often associated with hypertension and imparts even greater risk for cardiovascular outcomes than hypertension. Hypertension act as a dominant risk factor for CVD in patients with CKD, and it is almost inevitable that CKD patients will have hypertension. The elevation of blood pressure is related to retention of sodium, stimulation of the renin-angiotensin aldosterone system as well as sympathetic activation. The elevated catecholamine release in CKD has also been associated with CVD risk. Cardiac damage caused by hypertension in CKD patients is thought to be *via* LVH induction [6].

Drug utilization evaluation is a comprehensive review of patient's prescriptions against pre-determined standards to ensure its appropriateness for better clinical outcomes. We considered JNC 7 and KDOQI guidelines as standard therapy for treating hypertensive patients with CKD [7]. The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC) stated that Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensine receptor blockers (ARBs) along with loop diuretics are important component of most regimens to control BP in CKD patients. The JNC seventh report recommended that the BP in diabetics should be controlled to levels of 130/80 mmHg or lower. Rigorous control of BP is needed for reducing the progression of diabetic nephropathy to end-stage renal disease (ESRD). In hypertensive patients with chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) < 60 mL/min, the JNC seventh report recommended a goal BP of ≤ 130/80 mmHg and a need for using more than one anti-hypertensive drug to achieve this goal [8].

Rational use of drugs is important in CKD patients to prevent the progressions of disease as well as the development of CVD. Hence, we performed the study to observe the appropriate utilization of antihypertensive drugs according to JNC 7 guidelines. In addition, we also determined the number of drugs prescribed in generic name and use of contraindicated drugs.

MATERIAL AND METHODS: A retrospective observational study was conducted in inpatient nephrology department of BBR Hospital, Balanagar, Hyderabad from Sep 2016 to Feb 2017. Institutional human ethical committee approval (IEC/SIIP/03-0002) was taken prior to initiating the study. Cases of CKD patients prescribed with antihypertensive agents who had attended the study location in the past one year were collected randomly from the medical record room. A total of 155 cases were collected during the study period.

Inclusion Criteria: Subjects who were diagnosed with CKD along with history of hypertension above the age of 18 years of both genders were included.

Exclusion Criteria: Subjects with kidney diseases other than CKD, pregnant and lactating women, children, patients with surgical conditions like kidney stones, tumors and trauma, who had psychiatric illness and who were not treated with antihypertensive drug, were not included in the study.

A predesigned data collection form was used to collect all the necessary data from the patient's case report. Patients diagnosed with CKD and suffering from Hypertension with or without Diabetes mellitus were randomly selected during the study period. All the data was entered into excel sheets for ease of analysis. Descriptive statistics were used to analyze the data.

The patients were classified based on the hypertensive stages, age-wise, gender wise distribution, co-morbidities like diabetic or non-diabetic and class of antihypertensive drug prescribed. The total number of antihypertensive drugs prescribed for each patient (diabetic as well as non-diabetic) was found out. The drugs were categorized into their pharmacological classes and predominant classes prescribed were ruled out. Generic vs. brand names antihypertensive drugs were noted and compared. Prescriptions were analyzed to find out the use of contraindicated drugs and presence of polypharmcy.

RESULTS AND DISCUSSION: A total of 155 patients were included in the study. Their age wise distribution is as follows:

GFR deteriorates commonly with increasing age. By 6th decade it declines at a rate of 1 - 2 ml/min per year. If the systolic BP is uncontrolled the deterioration may raises up to 4-8ml/min per year leading to ESRD. The progressive renal failure can further worsen the uncontrolled HTN due to volume expansion and increases systemic vascular resistance. Hence, it is important to maintain the HTN within the limits specified in guidelines to slowdown the progression of renal disease and reduce cardiovascular morbidity and mortality [8]. In our observation, most patients belong to the age group of >60 years (49.03%) **Table 1** and the prevalence of the disease is more in males 99(63.87%) than in females (36.12%) **Table 2** which coincides with various past studies like elhami *et al*., where males are 70(58.33%), females are 50 (41.66%) with CKD [9].

TABLE 1: AGE WISE DISTRIBUTION OF PATIENTS

Age	Number of patients (n = 155)	Percentage (%)
20-30	5	3.22%
31-40	12	7.741%
41-50	22	14.1%
51-60	40	25.80%
>60	76	49.03%

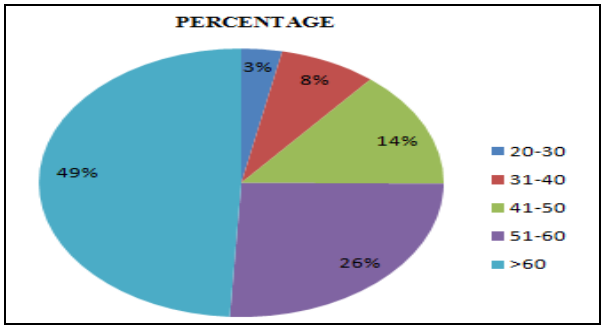

FIG. 1: AGE WISE DISTRIBUTION OF PATIENTS

TABLE 2: DEMOGRAPHIC DATA AND CLINICAL CHARACTERISTIC OF STUDY POPULATION (n = 155)

Parameter	Range	No. of patients	Percentage (%)
Sex			
•Male		99	63.87%
•Female		56	36.12%
Systolic B.P (mmHg)	<130 or =130	65	41.93%
	>130	88	56.77%
Diastolic B.P (mmHg)	<80 or =80	85	54.83%
	>80	68	43.87%
RBS	<200mg/dl	48	30.96%
	>200 mg/dl	107	69.03%
Serum creatinine	• 2-3mg/dl	83	53.54%
	• 3-5mg/dl	44	23.38%
	• >5mg/dl	27	17.41%

This study showed that out of 99 male patients 49(49.49%) had stage - 1 HTN, 45(45.5%) had stage - 2 HTN and 5(5.05%) had severe HTN **Table 3** where according to study done by Mahalaxmi *et al*., out of 299 male patients 132(44.14%) had stage - 1 HTN, 139(46.48%) had stage - 2 HTN, 28(9.36%) had severe HTN patient [10]. Out of 56 female patients 24(42.8%) had stage - 1 HTN, 27(48.2%) had stage - 2 HTN, 5(8.92%) had severe HTN which differs from Mahalaxmi *et al*., where out of 156 female patients 85(54.48%) are on stage - 1 HTN, 52 patients are on stage - 2 HTN, 19(12.17%) are on severe HTN. The differences can be attributed to the different population characteristics and variabilities.

TABLE 3: DISTRIBUTION OF PATIENTS AMONG VARIOUS STAGES OF HYPERTENSION

Stages of hypertension	Number of hypertensive patients	Percentage (%)
Stage -1	73	47.09
Stage -2	72	46.45
Severe	10	6.45

Though serum creatinine is not an ideal indicator for kidney function, it acts as a marker for diagnosing renal insufficiency. This study showed **Table 4** that 80(53.54%) of total patients had (S. Cr 2 - 3mg/dl) and 44(23.38%) of patients had (S. Cr 3 - 5 mg/dl) and 27(17.41%) of patients (S. Cr >5 mg/dl) which indicates the reduced renal function.

TABLE 4: GENDER WISE DISTRIBUTION AMONG VARIOUS STAGES OF HYPERTENSION

	Stage -1	Stage-2	Severe
Male (n=99)	49(49.49)	45(45.5)	5(5.05)
Female (n=56)	24(42.8)	27(48.2)	5(8.92)

Out of 302 drugs prescribed for 155 patients with CKD, most common drugs were diuretics followed by calcium channel blockers and beta blockers. The same pattern was observed in CKD patients with diabetes.

Out of 302 drugs prescribed for hypertensive patients with CKD, most common drugs **Table 5** are diuretics, 123(40.71%), 80(26.48%) calcium channel blocker, 46(15.22%) beta blockers, 18(5.96%) alpha adrenergic blockers, 17(5.62%) ARB'S, 14(4.63%) alpha agonist, 3(0.99%) ACE inhibitors, and 1(0.33%) is monoxidine which coincide with the study done by Pavithra *et al*., [11]

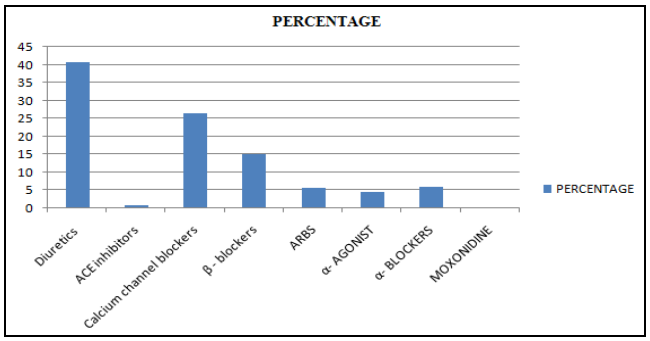

FIG. 2: DRUG UTILIZATION PATTERN OF ANTI-HYPERTENSIVE DRUGS IN CKD

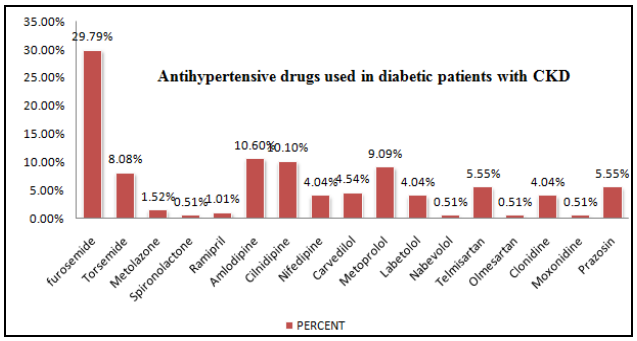

FIG. 3: ANTI - HYPERTENSIVE DRUGS USED IN DIABETIC PATIENTS WITH CKD

TABLE 5: PATTERN OF ANTIHYPERTENSIVE DRUGS PRESCRIBED IN CKD PATIENTS

Drug Groups	Frequency	Percentage (%)
Diuretics		
Furosemide	94	31.12%
Torsemide	24	7.94%
Metolazone	4	1.32%
Spironolactone	1	0.33%
Ace Inhibitors		
Ramipril	3	0.99%
Calcium Channel Blockers:		
Amlodipine	36	11.92%
Cilnidipine	24	7.94%
Nifedipine	20	6.62%
β – Blockers		
Metoprolol	30	9.93%
Carvedilol	11	3.64%
Labetolol	4	1.32%
Nabevolol	1	0.33%
ARB'S		
Telmisartan	16	5.29%
Olmesartan	1	0.33%
α – agonist		
Clonidine	14	4.63%
Moxonidine	1	0.33%
α-Adrenergic Blocker		
Prazosin	18	5.96%
Total	302	100%

TABLE 6: PATTERN OF ANTIHYPERTENSIVE DRUGS PRESCRIBED IN DIABETIC PATIENTS WITH CKD

Drug Groups	Frequency	Percentage (%)
Diuretics		
Furosemide	59	29.79%
Torsemide	16	8.080%
Metolazone	3	1.515%
Spironolactone	1	0.505%
Ace Inhibitors		
Ramipril	2	1.010%
Calcium Channel Blockers:		
Amlodipine	21	10.60%
Cilnidipine	20	10.10%
Nifedipine	8	4.04%
β – Blockers		
Metoprolol	18	9.09%
Carvedilol	9	4.54%
Labetolol	8	4.04%
Nabevolol	1	0.505%
ARB'S		
Telmisartan	11	5.55%
Olmesartan	1	0.505%
α – agonist		
Clonidine	8	4.04%%
Moxonidine	1	0.505%
α- Adrenergic Blocker		
Prazosin	11	5.96%
Total	198	100%

This study showed that out of 155 hypertensive CKD patients **Table 6**, 98 patients are with diabetes and 198 antihypertensive drugs are prescribed to them. Most common drugs are diuretics 79(39.89%), Calcium channel blockers 49(24.74%), beta blockers 36(18.17%), ARB's 12(6.05%), Prazosin 11(5.96%), Clonidine 8(4.04%), ACE inhibitors 2(1.010%) and moxonidine 1(0.505%) which differs from results of study done by elahe elhami [9] where most common drugs prescribed are ACE inhibitors (39.78%), Diuretic (36.15%), calcium channel blockers (8.75%), beta-blockers (8.32%) and ARB'S (4.82%).

Diuretics were prescribed predominantly in both diabetic and non-diabetic kidney disease. Diuretics not only control BP, but also increases effectiveness of other antihypertensive drugs and are affordable. They also decrease the risk of developing cardiovascular diseases, but ACE inhibitors are far more superior in this regard. JNC 7 guidelines and KDOQI guidelines suggest the use of either ACE inhibitors or ARBs along with diuretics (loop diuretics) to control BP in CKD patients. ACE inhibitors or ARBs induce dilation of efferent arterioles in renal glomerulus, resulting in reduced intraglomerular pressure, and inhibit proinflammatory and proliferative actions

exerted by angiotensin II. JNC 7 guidelines also suggest the use of ACE inhibitors or ARBs as first line drugs in treating HTN in CKD patients, especially with Diabetes. But these drugs are associated with acute renal failure or hyperkalemia when given to elderly and ESRD patients who require constant monitoring [12]. β - blockers reduce insulin sensitivity, except for some newer substances, and therefore they should be avoided in patients with diabetes or impaired glucose tolerance.

TABLE 7: NUMBER OF ANTIHYPERTENSIVE DRUGS PRESCRIBED ACCORDING TO GENERIC AND BRAND NAMES

Antihypertensive Drugs	Frequency	Percentage
Generic	106	35%
Brand	196	65%

Multidrug regimen is needed in controlling the BP at the desired level and to prevent the occurrence of CVDs. In our study **Table 8**, most patients were prescribed multidrug regimen to control the BP in the desired range.

The reported use of mono and combination use of ACE inhibitors was lower than reported by elhami *et al*., in treating diabetic hypertensive patients [9]. This study showed that 41.3% of patients are on monotherapy, 40.7% are on two drug therapy, 14.8% are on three drug therapy, 3.32% are on four drug therapy which differs from study done by elhami *et al*., where monotherapy was prescribed to 36% of patients, 50% were on two drug therapy, 20% are on three drug therapy [9]. Diuretics and calcium channel blockers were most common drugs prescribed in monotherapy and two drug therapy, β - blockers ranked third followed by ARB's, alpha adrenergic blockers and ACE inhibitors. The results coincide with the study done by Pavithra *et al*.,[11] where 80% of dual therapy was done using calcium channel blockers and diuretic combination followed by diuretics and β – blockers. This study differs from study by elhami *et al*., where diuretic ranked second followed by calcium channel blockers and ARB's [9]. These differences can be attributed to the inter subject variabilities among the patients in the two studies and physicians current clinical judgment. Use of multidrug therapy is based on patients BP, age, co-morbidities, whether BP is under control with the current drugs or not and the progression of CKD *etc*.

TABLE 8: PATTERN OF ANTIHYPERTENSIVE THERAPY IN DIABETIC AND NON-DIABETIC PATIENTS WITH CKD

Drug class	No. of patients with DM (n=98)	No. of patients without DM (n=57)
Monotherapy		
Diuretics	22(22.4%)	14(24.5%)
Calcum Channel Blockers	11(11.22%)	7(1.75%)
β -Blockers	5(5.10%)	3(5.26%)
α – Blockers	1(1.02%)	--
Moxonidine	1(1.02%)	--
Total	40	24
Two Drug Therapy		
ARB'S + Diuretics	6(6.12%)	-
β -Blockers+ Diuretics	8(8.16%)	3(5.26%)
Calcium Channel Blockers(CCB) + β-Blockers	6(6.12%)	3(5.26%)
CCB+Diuretic	13(13.26%)	12(21.0%)
ARB'S + CCB	3(3.06%)	1(1.75%)
α-Blockers + Diuretic	1(1.02%)	1(1.75%)
CCB+ α –Agonist	1(1.02%)	-
α – Adrenergic Blocker + CCB	2(2.04%)	-
α -Blocker +β-Blocker	1(1.02%)	-
Diuretic + Ace Inhibitor	-	1(1.75%)
Diuretic+ α- Agonist	-	1(1.75%)
Total	41	22
Three Drug Therapy		
Diuretic + α-Agonist + α-Blocker	1(1.02%)	1(1.75%)
ARB'S + CCB + Diuretic	3(3.06%)	1(1.75%)
ACE + β-Blocker + Diuretic	2(2.04%)	-
CCB + β-Blocker + Diuretic	5(5.10%)	2(3.50%)
α-Blocker + β-Blocker + Diuretic	1(1.02%)	2(3.50%)
Diuretic + CCB + α-Agonist	1(1.02%)	2(3.50%)
β-Blocker + ARB'S + Diuretic	1(1.02%)	-
β-Blocker + CCB + α-Blocker	1(1.02%)	-
Total	15	8
Four Drug Therapy		
Diuretic + α-Agonist + CCB + α-Blocker	1(1.02%)	2(3.50%)
ARB'S + CCB+ α-Agonist + Diuretic	1(1.02%)	-
α-Agonist + CCB+ β-Blocker + α-Blocker	-	1(3.50%)
Total	2	3

The combination of these drugs provides added advantage because different classes of drugs have different mechanism of action for reduction in blood pressure. They are also beneficial in decreasing the adverse effects of each other. This study also showed that there was significant difference in control of systolic as well as diastolic blood pressure in patients without reduced renal function than in patients with reduced renal function. The patients were prescribed medications with accurate doses according to WHO guidelines.

Prescribing by generic name allows the flexibility of stocking and dispensing of various brands of particular drug that are cheaper and are effective as proprietary brands. The percentage of generics prescribed in our study (35%) is very low and it increases the economical cost to the patient **Table 7**. There were no prescriptions containing any contraindicated drugs. As the patients are having co-morbidities, polypharmacy is inevitably seen in most of the prescriptions.

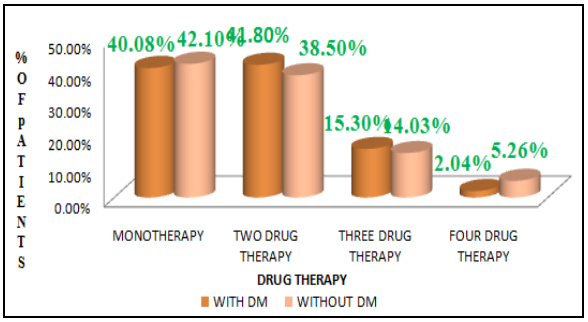

FIG. 4: MULTIPLE DRUG THERAPY IN CKD PATIENTS

CONCLUSION: Our study showed that majority of patients needed multiple drug therapy to delay the progress of disease. All drugs were prescribed at their appropriate doses according to JNC 7 guidelines and no contraindicated drugs were prescribed in any one of the 155 prescriptions. Diuretics were prescribed mostly in both DM and non DM hypertensive patients with CKD. They are helpful both by decreasing the fluid volume and blood pressure. They also decrease the incidence of cardiovascular diseases in future which occurs during the progression of CKD with hypertension. But according to JNC 7 and KDOQI guidelines the choice of drugs for hypertensive CKD patients are ACE inhibitors or ARB's with diuretics. Because of the many constraints, re-evaluation with the advised drugs, its review and feedback was not done.

These drugs can be evaluated for their therapeutic benefit in this specific population at this hospital and the results can be reviewed to provide further advice. Polypharmacy was observed in almost all prescriptions and is inevitable in these patients because of disease burden and possible further complications. Active participation of clinical pharmacist and his/her dedication in clinical pharmacy services like drug therapy monitoring, drug information services, patient counselling, ADR detection and management will definitely improve the outcome of treatment. Branded drugs were prescribed in most of the prescriptions which increases the cost of treatment. Hence, prescribing generic drugs should be encouraged at the hospital.

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CONFLICT OF INTEREST: Nil

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