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Original Article

THE IMPACT OF ANTIHYPERTENSIVE DRUG THERAPY IN PATIENTS WITH CHRONIC KIDNEY DISEASE: A PROSPECTIVE OBSERVATIONAL COHORT STUDY

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ABSTRACT

Objective: Hypertension (HTN) is both a cause and an effect of chronic kidney disease (CKD). To adequately control blood pressure (BP) in CKD, choosing antihypertensive strategies with the highest nephro-protective effect is crucial for preventing or reversing end-stage renal disease (ESRD) progression and reducing cardiovascular disease (CVD) risk. The present study was therefore designed to evaluate the impact of clinical use of antihypertensive drug therapy in patients with CKD and ESRD.

Methods: It is a prospective observational cohort study. The patients were divided into two cohorts i.e.; non-dialysis dependent (NDD) and dialysis-dependent (DD) CKD. This study was conducted for six months in the Nephrology department, Osmania General Hospital, Hyderabad, India. The data collected and entered into Microsoft Excel (2007) and mean, SD and range were calculated using SPSS version 25.

Results: Antihypertensive drugs were prescribed alone or in combination based on the co-morbidities associated with CKD and HTN. Loop diuretics (Furosemide and Torsemide) and calcium channel blocker (Amlodipine, Nifedipine and Cilnidipine) were most commonly prescribed antihypertensive drugs. Triple therapy (44.11%) was prescribed mostly in both the cohorts (NDD = 16.66%+DD = 27.45%) of which calcium channel blockers+loop diuretic+sympatholytic accounts for 19.16% (NDD = 5.88%+DD = 13.73%).

Conclusion: The practice of prescribing antihypertensive drugs for the management of HTN and to achieve BP targets in CKD and ESRD remains uncertain. The development of new and revised guidelines is needed to reduce inappropriate variations in practice and promote better delivery of evidence-based treatment.

Keywords: Chronic kidney disease (CKD), Non-dialysis dependent (NDD), Dialysis dependent (DD), National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI), Kidney Disease: Improving Global Outcomes (KDIGO), Joint National Committee (JNC)

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INTRODUCTION

Chronic kidney disease (CKD) with its high prevalence, morbidity and mortality, is an important public health challenge [1]. According to the 2012 KDIGO clinical practice guidelines, CKD is defined as 'abnormalities of kidney structure or function, present for>3 mo, with implications for health.' Criteria for CKD (Either of the following presents for>3 mo): Markers of kidney damage (one or more): Albuminuria (ACR≥ 30 mg/g), Urine sediment abnormalities, Electrolyte and other abnormalities due to tubular disorders, Pathological abnormalities detected by histology, Structural abnormalities detected by imaging, History of kidney transplantation; Decreased glomerular filtration rate (GFR)<60 ml/min/1.73m^2 [2].

CKD and ESRD represent worldwide public health problems with an epidemic extent [3, 4]. From 1990-2013 the age-adjusted death rates attributable to CKD increased by 36.9% in 188 countries surveyed and CKD is now the 19th leading cause of life years lost [5]. In India, the incidence of CKD is rising and as per estimates from 2006, the age-adjusted incidence rate of ESRD is 229 per million population [6]. In 2015, CKD affected about 323 million people globally and resulted in 1.2 million deaths, up from 4,09,000 in 1990 [7]. The causes that contribute to the greatest number of deaths are hypertension at 5,50,000 followed by diabetes at 4,18,000 and glomerulonephritis at 2,38,000 [8].

Hypertension (HTN) is a major risk factor for cardiovascular and renal disease. Conversely, CKD is the most common form of secondary hypertension [9]. HTN is present in 50% to 80% of patients with CKD [10] defined as the persistent elevation of systolic blood pressure (SBP)≥140 m mHg and diastolic blood pressure (DBP) ≥90 mmHg [11]. It is a strong independent, modifiable risk factor for CKD and contributes to the disease itself or, most commonly, to its progression [12]. It may develop early during the CKD and may contribute to adverse outcomes such as worsening of renal function or progression of kidney disease towards ESRD, development of cardiovascular diseases (CVD) such as heart attack and stroke and high cardiovascular morbidity and mortality [13-15].

Thus, HTN and CKD are inextricably linked with both cause and effect relationships [16]. It is well established that albuminuria and reduced GFR, in both diabetic and non-diabetic hypertensive CKD patients, are major cardiovascular risk factors and many older patients develop or die from cardiovascular disease rather than progress to ESRD [17, 18]. In particular, this may be due to inadequate control of HTN in patients with CKD [19].

There is some evidence that BP should be reduced below 130/85 mm Hg in patients with diabetic and non-diabetic nephropathies and<125/75 mm Hg in patients with non-diabetic nephropathies and proteinuria>1 g/day and the available data suggests that tight BP control (BP<140/80 mm Hg) can reduce the risk of cardiovascular complications in hypertensive patients with type 2 diabetes mellitus [20]. The JNC VIII guidelines for HTN in patients>18 y old with CKD recommend a goal BP of<140/90 mmHg regardless of CKD stage or proteinuria. Other recommendations, including those by the KDIGO study in 2012, recommend a similar goal blood pressure of<140/90 mmHg in most CKD patients, but stricter control (<130/80 mmHg) in those with>30 mg/day proteinuria [21].

Aggressive treatment of HTN has been a key component [22] relevant at all stages of the disease, irrespective of the underlying cause [23, 25] as it is associated with improved cardiovascular outcomes in both CKD and ESRD [24]. Antihypertensive drugs are therefore recommended in patients with CKD with or without HTN as these agents provide cardio-protective and reno-protective

benefits [25]. Antihypertensive drugs are therefore used in CKD to (1) Reduce BP; (2) Reduce the risk of CVD, and (3) slow the progression of kidney disease [26]. Recent guidelines for the treatment of HTN in CKD suggest the use of a variety of antihypertensive drugs to achieve the desired BP levels. Usually, a combination of two or more antihypertensive drugs is required to control HTN. Antihypertensive treatment is individualized to each patient depending on the age, severity of albuminuria, tolerance, compliance and specific clinical features [17, 21, 27].

In the present study, current evidence supporting treatment of HTN with antihypertensive drugs in CKD was reviewed and the study was therefore designed and performed to evaluate the impact of antihypertensive drug therapy in patients with CKD (Non-dialysis dependent) and ESRD (Dialysis dependent) in association with the patients' clinical or disease outcomes.

MATERIALS AND METHODS

The present study carried out to determine the impact of antihypertensive drug therapy in CKD patients with HTN. Ethical clearance was obtained from the Institutional Ethics Committee (No. MCP/IEC/PD/PR/30) before the commencement of the project. The duration of the study was six (6) months. The study was carried out in the Inpatient Department of Nephrology, Osmania General Hospital, a tertiary care teaching hospital, Hyderabad, Telangana, India.

Study design

This is a hospital-based prospective observational cohort study. The patients were divided into two cohorts i.e.; non-dialysis dependent (NDD) and Dialysis dependent (DD) CKD based on the history of albuminuria, estimated glomerular filtration rate (eGFR) and the requirement for dialysis.

Study population

The study was conducted on 120 patients with presumed and/or confirmed CKD with HTN, but 18 patients were excluded based on the inclusion and exclusion criteria. 06 patients were lost to follow up, 12 patients were excluded after clinical judgment (AKI, Autoimmune disease, Current Infection, and Lactating woman; age<18). The remaining 102 patients were evaluated during the study.

Inclusion and exclusion criteria

After written informed consent was obtained following national guidelines, the subjects for the study were selected based on the following criteria that include: Patients of either sex, Age group ≥18years, Patients diagnosed as CKD Stages III-V and ESRD patients on hemodialysis. Terminally ill patients co-infected with HIV or hepatitis or with any infective conditions or with any autoimmune diseases, Patients of age group<18yrs, Patients with acute kidney injury (AKI), Surgical conditions like kidney stones, tumors, trauma and CKD patients with renal transplant, Pregnant and lactating women, individuals who are not willing to give consent were excluded.

Data collection

Proforma was designed covering all the necessary parameters. Data was collected from medical record sheet, patients and their attendants. The study related Physical examination, Clinical and Biochemical findings including BP (SBP and DBP), eGFR, serum electrolytes, serum creatinine, serum urea, albuminuria along with radiological findings including USG, X-ray and CT scan of the abdomen were documented and assessed at the time of admission and discharge as per the available literature. The data was used to determine the impact of antihypertensive drugs on the study cohorts.

Data analysis

The data was recorded, tabulated using Microsoft Excel 2007 version and descriptive analysis (mean, SD and range) performed using SPSS version 25.

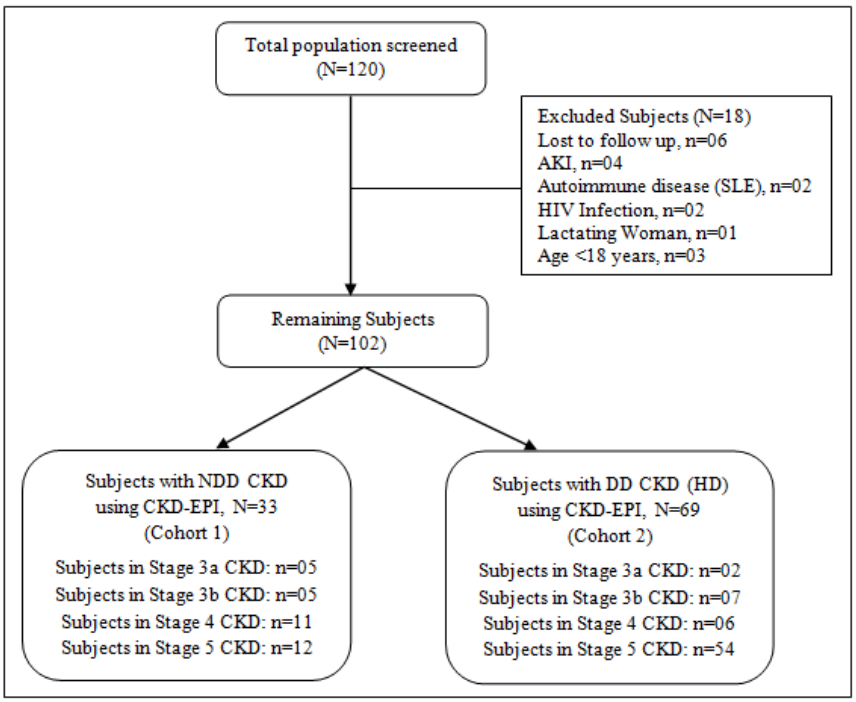

Fig. 1: Flow Chart of the Study cohort, AKI: Acute Kidney Injury; HIV: Human Immune Virus; NDD: Non-Dialysis Dependent; DD: Dialysis Dependent; HD: Haemodialysis; CKD-EPI: (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation (2009)

RESULTS

A total of 102 patients were observed to study the cardio-protective and reno-protective effect of antihypertensive drugs during their stay at the hospital. These patients were divided into two cohorts viz. non-dialysis dependent (NDD) CKD (Cohort 1) and Dialysis dependent (DD) CKD (Cohort 2) depending upon the extent of kidney damage and dialysis required.

Table 1: Patients' characteristics in two cohort groups

Characteristics	NDD-CKD (Cohort 1) N = 33 No. of Patients (%)		DD-CKD (Cohort 2) N = 69 No. of Patients (%)	
Age (years)	**Male (n = 22)**	**Female (n = 11)**	**Male (n = 37)**	**Female (n = 32)**
18-27	2 (1.96%)	1 (0.98%)	3 (2.94%)	2 (1.96%)
28-37	5 (4.90%)	1 (0.98%)	6 (5.88%)	3 (2.94%)
38-47	3 (2.94%)	4 (3.92%)	11 (10.78%)	5 (4.90%)
48-57	1 (0.98%)	1 (0.98%)	8 (7.84%)	6 (5.88%)
58-67	10 (9.80%)	4 (3.92%)	7 (6.86%)	11 (10.78%)
≥68	1 (0.98%)	0 (0.00%)	2 (1.96%)	5 (4.90%)
Social History				
Current Smoker	3 (2.94%)	0 (0.00%)	6 (5.88%)	1 (0.98%)
Ex-Smoker	3 (2.94%)	2 (1.96%)	2 (1.96%)	0 (0.00%)
Non smoker	16 (15.69%)	9 (8.82%)	29 (28.43%)	31 (30.39%)
Co-morbidities				
HTN (as cause)	22 (21.57%)	10 (9.80%)	33 (32.35%)	32 (31.37%)
Denovo HTN (as effect)	0 (0.00%)	1 (0.98%)	4 (3.92%)	0 (0.00%)
Diabetes	10 (9.80%)	13 (12.75%)	8 (7.84%)	12 (11.76%)
CVD	11 (10.78%)	10 (9.80%)	16 (15.69%)	28 (27.45%)
Stroke	0 (0.00%)	1 (0.98%)	0 (0.00%)	2 (1.96%)
Staging of CKD based on eGFR and Albuminuria				
G3a-A2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
G3a-A3	4 (3.92%)	1 (0.98%)	1 (0.98%)	1 (0.98%)
G3b-A2	1 (0.98%)	1 (0.98%)	1 (0.98%)	0 (0.00%)
G3b-A3	3 (2.94%)	0 (0.00%)	4 (3.92%)	2 (1.96%)
G4-A2	0 (0.00%)	0 (0.00%)	1 (0.98%)	0 (0.00%)
G4-A3	10 (9.80%)	1 (0.98%)	3 (2.94%)	2 (1.96%)
G5-A2	2 (1.96%)	0 (0.00%)	0 (0.00%)	1 (0.98%)
G5-A3	2 (1.96%)	8 (7.84%)	27 (26.47%)	26 (25.49%)

HTN–Hypertension, CVD–Cardiovascular Disease, NDD–Non-Dialysis Dependent, DD–Dialysis Dependent, CKD-Chronic Kidney Disease, eGFR–Estimated Glomerular Filtration Rate.

The mean age of CKD in NDD patients was 49.30±15.20 (Range=68-20) and in DD patients were 50.25±14.69 (Range=80-20). Majority of the patients (57.84%) were male in both the study cohorts (NDD=21.57% and DD=36.27%). In study cohorts, n=97(95.10%) were hypertensive (HTN as a CAUSE) and were receiving antihypertensive medications and n=5(04.90%) were newly diagnosed with HTN (HTN as an EFFECT). Most of the patients in both the cohorts were at G5/A3 stage (61.76%) followed by G4/A3 (15.69%).

Table 2: Percentage of antihypertensive drugs prescribed

Antihypertensive drugs prescribed			Percentage (%)
RAS Antagonist	Angiotensin Converting Enzyme Inhibitors (ACEI)	Enalapril	26.47%
	Angiotensin II Receptor Blockers (ARB)	Telmisartan	2.94%
Adrenergic Antagonists	Alpha Blockers (AB)	Prazosin	2.94%
	Beta Blockers (BB)	Atenolol	8.82%
		Metoprolol	22.55%
	Alpha+Beta Blockers (ABB)	Labetalol	2.94%
Adrenergic Agonists	Centrally Acting Alpha$_2$ Agonist/Sympatholytic (CAAA/SYM)	Clonidine	27.45%
Calcium Channel Blockers (CCB)	Dihydropyridines (DHP)	Amlodipine	81.37%
		Nifedipine	7.84%
		Cilnidipine	1.96%
Diuretics (D)	Loop	Furosemide	84.30%
		Torsemide	4.90%
	Thiazide Like	Metolazone	1.96%
	Potassium Sparing	Spironolactone	2.94%

In both, the study cohorts, the most commonly prescribed class of antihypertensive drugs was diuretics (D) (93.40%) followed by calcium channel blockers (CCBs) (93.17%). Furosemide (84.30%) and Amlodipine (81.37%) were the most commonly prescribed antihypertensive drugs followed by Clonidine (27.45%) in combination with other antihypertensive drugs in the study cohorts.

Antihypertensive drugs were prescribed alone or in combination based on the co-morbidities associated with CKD and HTN. All the patients (N=102) in the study were diagnosed with CKD and HTN with the evidence of albuminuria. Triple therapy (44.11%) was prescribed mostly in both the Cohorts (NDD = 16.66%+DD = 27.45%).

Table 3: Percentage of antihypertensive drugs prescribed for the treatment of hypertension with associated co-morbidities in cohort 1 and cohort 2

Hypertension and associated Co-morbidities	Antihypertensive therapy prescribed	Therapy received by NDD (%)	Therapy received by DD (%)
CKD+HTN+Albuminuria (X = 102)	CCB (DHP)	0.98%	4.90%
X+Fluid Overload	CCB (DHP)+D (loop)	1.96%	12.75%
	CCB+D (loop)+SYM	0.00%	1.96%
	AB+D (loop)+SYM	0.00%	0.98%
	CCB (DHP)+D (loop)+ABB	0.00%	2.94%
	CCB (DHP)+D (loop)+BB+SYM	0.00%	3.92%
X+DM	CCB (DHP)+BB	0.98%	0.98%
X+CAD/PVD	CCB (DHP)+BB	0.98%	0.00%
	CCB (DHP)+RAS	0.98%	0.00%
X+Fluid overload+DM	BB+D (loop)	0.98%	0.00%
	CCB (DHP)+D (loop)+RAS	4.90%	0.98%
	RAS+D (loop)+BB	0.98%	1.96%
	CCB (DHP)+D (loop)+BB± D (Potassium Sparing)	0.98%	11.76%
X+Fluid overload±LVD/lVH	CCB (DHP)+D (loop)+SYM	5.88%	13.73%
X+Fluid overload+CCF	CCB (DHP)+D (loop)+RAS+SYM	0.98%	0.00%
	BB+D (loop)+RAS+SYM	0.00%	0.98%
X+DM+CCF	CCB (DHP)+D (loop)+RAS	0.98%	0.00%
	3Ds (Loop, Potassium Sparing, Thiazide Like)+RAS+CCB	0.00%	0.98%
X+DM+CAD/PVD	RAS+BB	1.96%	0.00%
X+CCF/HF+DM+	D (loop)+SYM	0.00%	0.98%
CAD/PVD	CCB (DHP)+D (loop)+RAS+BB	2.94%	3.92%
X+DM+LVD/lVH+CAD	D (loop)+BB	0.00%	0.98%
X+Fluid overload+DM+CAD/PVD	D (loop)+BB	0.98%	0.00%
	CCB (DHP)+D (loop)+RAS	0.98%	2.94%
X+Fluid overload+DM+Stroke	RAS+CCB (DHP)+D (loop)+BB	0.98%	0.00%
X+DM+LVD/lVH+CAD+Angina	RAS+D (loop)+BB	1.96%	0.00%
X+Fluid overload+DM+CAD/PVD+Stroke	CCB (DHP)+D (loop)	0.98%	0.00%

HTN = Hypertension, X = Hypertension+Albuminuria, DM = Diabetes Mellitus, LVD = Left Ventricular Dysfunction, LVH = Left Ventricular Hypertrophy, CAD = Coronary Artery Disease, PVD = Peripheral Vascular Disease, CCF = Congestive Cardiac Failure, HF = Heart Failure; AB = Alpha Blocker, ABB = Alpha+Beta Blocker, BB = Beta Blocker, CCB = Calcium Channel Blocker, DHP = Dihydropyridine, D = Diuretic, RAS = Renin Angiotensin System.

Table 4: Indication for antihypertensive drug therapy prescribed to the study cohorts

Antihypertensive drug	Indication
AB (Prazosin), ABB (Labetalol), D (Metolazone)	Resistant Hypertension in DD patients
ACEI (Enalapril), ARB (Telmisartan)	HTN, DM, Proteinuria and Decreased eGFR, CCF, CAD/PVD, CVA,
BB (Atenolol, Metoprolol)	HTN, DM to prevent CV complications, Angina, CCF,
CCBs (Amlodipine, Nifedipine, Cilnidipine)	HTN, Angina, CVA
D (Furosemide and Torsemide)	HTN, Fluid Overload, CCF,
SYM (Clonidine)	HTN, Pulmonary oedema and LVH/lVD
Potassium Sparing Diuretic (Spironolactone)	HTN, Drug-Induced Hypokalaemia

Table 5: Assessment of blood pressure during admission and discharge in cohort 1 and cohort 2 receiving antihypertensive therapy

BP (mmHg) (SYSTOLIC/DIASTOLIC)	During admission No. of patients (Mean BP)		During discharge No. of patients (Mean BP)	
	NDD	DD	NDD	DD
Normal (≤ 120/80)	1 (110)/ 0 (0)	0 (0)/1 (70)	2 (110)/3 (70)	3 (110)/1 (60)
Pre-Hypertension (120-139/80-89)	10 (130)/7 (80)	10 (130)/8 (80)	19 (127.4)/19 (80)	46 (127.8)/35 (80)
Stage-1 Hypertension (140-159/90-99)	9 (145.5)/14 (90)	35 (147.1)/ 37 (90)	9 (144.4)/10 (90)	20 (141.5)/33 (90)
Stage-2 Hypertension (≥ 160/100)	13 (180)/12 (106.6)	24 (176.7)/23 (104.5)	3 (160)/1 (100)	0 (0)/0 (0)

n = No. of Patients.

In study cohorts, BP was calculated and assessed during hospital admission and discharge based on the JNC VIII 2014 guidelines for the staging of HTN. Cohort 1 and 2 at the Stage-2 HTN and Cohort 2 at the Stage-1 HTN (during hospital admission) have found to be effectively responded to the antihypertensive therapy prescribed.

DISCUSSION

There is a strong association between CKD and an elevated BP whereby each can cause or aggravate the other. A higher BP is generally associated with a higher CVD risk, making BP lowering an attractive goal to reduce CV morbidity and mortality. Thus, BP control is fundamental to the care of patients with CKD and is relevant at all stages of CKD (NDD or DD) regardless of the underlying cause [23].

The predominance of the male in the study cohorts is similar to earlier studies [6, 17]. The prevalence of hypertension gradually increases as renal function deteriorates, and a high BP condition is almost universal in patients who progress to ESRD [28]. In the present study, the majority of the population were receiving haemodialysis apart from

antihypertensive therapy. These patients were grouped under dialysis-dependent (DD) CKD Cohort. 67.64% of patients were DD and 32.36% were non-dialysis dependent (NDD) CKD patients.

Multimorbidity is associated with CKD and HTN, of which 67.25% accounts for CVDs followed by DM (42.15%). Co-morbidities are important because they may impact on treatment burden, medications management, quality of life, and survival [29]. Therefore, antihypertensive drugs were prescribed to the study cohorts based on the co-morbidities associated.

Patients with CKD are more likely to die, largely from CVD than require dialysis. Once they develop ESRD, dialysis patients have eight times the mortality rate of their age-matched counterparts in the general population, with cardiovascular causes accounting for more than 50% of deaths. It is, therefore, critically important to control modifiable risk factors (e. g., hypertension) in this high-risk group [9].

The five classes of antihypertensive drugs prescribed to the cohorts were RAS antagonists, CCBs, BBs, Diuretics, and Sympatholytic. Loop diuretics (Furosemide and Torsemide) and calcium channel blocker (Amlodipine, Nifedipine and Cilnidipine) were the most commonly prescribed antihypertensive drugs. Furosemide accounts for 84.30% followed by Amlodipine 81.37%. The study shows the limited prescription of first-line therapy (RAS) (29.41%), which has been shown to delay the progression of chronic kidney disease (CKD) [27, 30]. In the study cohorts, BB (31.37%) (Metoprolol and Atenolol) were commonly prescribed in DM and DD patients than NDD patients [31].

The combination therapy most commonly prescribed in both the study cohorts was the triple therapy (44.11%) of which, CCB+loop diuretic+SYM regimen accounts for 19.16% (NDD = 5.88%+DD = 13.73%). In DD patients, the second most commonly prescribed combination therapy was dual therapy regimen, CCB+loop diuretic accounting for 12.75%, whereas the four-drug regimen as second and third most prescribed in NDD and DD respectively. The Antihypertensive drugs were individualized and prescribed based on the associated risk factors and co-morbidities in the study cohorts (table 6) [9, 26]. Monotherapy (Amlodipine alone) was found to be ineffective, unlike RAS antagonists for the treatment of HTN in CKD with proteinuria. It is found to agree with the earlier reports [32].

Most of the NDD and DD patients (93.04%) at Stage 2 and DD patients at Stage 1 HTN were achieved significant decrease in BP with Triple, Four-drug and Dual therapy in order. From NDD and DD cohorts respectively, (n= 21/21) 20.58%/20.58% and (n= 49/36) 48.03%/35.29% reached their (Systolic/Diastolic) BP goal of<130/80 mmHg; (n= 9/10) 8.82%/9.80% and (n= 20/33) 19.61%/32.35% reached their (Systolic/Diastolic) BP goal of<140/90 mmHg.

Findings

In the present study, the impact of five different classes of antihypertensive drugs was evaluated. The outcomes of dual, triple and polytherapy were found to be effective in lowering BP, slowing down the progression of CKD and reducing the incidence of CV events, unlike monotherapy. Calcium channel blockers (CCB) in combination with the other drugs have shown the best cardioprotective and renoprotective outcomes in the study cohorts. Use of beta-blockers (BB) or calcium channel blockers (CCB) and diuretics (D)±Sympatholytic steadily increased, whereas use of renin-angiotensin system (RAS) Antagonist decreased with advancing CKD. Angiotensin-converting enzyme (ACE) Inhibitor was replaced by angiotensin II receptor blocker (ARB) in elderly patients (>60 y) as the former is primarily renally eliminated, thus potentially leading to accumulation in renal impairment than ARB, eliminated hepatically. Labetalol other than Atenolol and Metoprolol was additionally being used as a dialyzable agent in dialysis-dependent CKD patients. Alpha-blockers like Prazosin and Sympatholytic like Clonidine and Diuretics caused postural hypotension in elderly patients; thus these drugs were used cautiously. Initiation of antihypertensive drug therapy other than the first-line therapy (RAS) in young patients resulted in the subsequent progression of CKD to ESRD and CV complications.

The study is limited by its sample size, unicentric nature, a short period of six months and few classes of drugs prescribed. Further follow-up of patients is needed to increase the understanding of long-term effects and outcomes.

CONCLUSION

In conclusion, the practice of prescribing antihypertensive drugs for the management of hypertension and to achieve blood pressure targets in chronic kidney disease (CKD) and end-stage renal disease (ESRD) remains uncertain. Although, the prescription of antihypertensive drugs has been based on the standard treatment guidelines (NKF KDOQI 2004 and KDIGO 2012), the development of new and revised guidelines suggesting novel and effective therapies is needed to reduce inappropriate variations in practice and promote better delivery of evidence-based treatment.

AUTHORS CONTRIBUTIONS

All authors contributed equally. All authors read and approved the final manuscript.

CONFLICTS OF INTERESTS

Declared none

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