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IMPACT OF DIURETIC USE ON BLOOD PRESSURE, AND RENAL FUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND HYPERTENSION

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ABSTRACT

Diuretics for the management of hypertension in the chronic kidney disease (CKD) population have been undervalued against other classes of antihypertensive medications for years. This study aimed to determine the prevalence of diuretic use, ascertain their prescribing pattern, and investigate their impact on blood pressure (BP) and renal function among patients with CKD and hypertension. The study was a one-year retrospective longitudinal study that included patients with CKD and hypertension who received care in a tertiary care hospital in Nigeria. A systematic random sampling technique was applied to collect data. Paired-samples-t test was used to compare the mean BP, creatinine level, and estimated glomerular filtration rate (eGFR) at baseline and three months, while the independent-t test was used to compare the mean differences of these parameters between those that had diuretics with or without other antihypertensive medications and those who had other antihypertensive medications, all at $p < 0.05$ statistically significant level. The prevalence of diuretic use was 80.3% with loop diuretics (97.6%) as the most commonly prescribed. Furosemide ranked first (77.8%) among all the individual diuretics prescribed. From baseline to 3 months, systolic BP and diastolic BP were significantly decreased by 32.3 mmHg, P<0.001, and 12.8 mmHg, P<0.001, respectively. Also, creatinine and eGFR were significantly decreased and increased by 180 µmol/L, P<0.001, and 1.7 mL/minutes/1.73m^2, P<0.001, respectively. An overwhelming proportion of the study population was prescribed diuretics mainly furosemide with or without other antihypertensive medications. Also, this study has shown that diuretics can impact BP and renal function positively among patients with CKD and hypertension.

Keywords: Blood Pressure; Chronic Kidney Disease **(**CKD); Diuretics; Estimated Glomerular Filtration Rate (eGFR); Renal Function

INTRODUCTION

Globally, chronic kidney disease (CKD) is becoming more common and is closely linked to incident cardiovascular diseases (CVDs). The great majority of patients with CKD suffer from hypertension, which can both cause and result from the disease. In people with CKD, controlling hypertension is crucial because it lowers the risk of CVDs and slows the disease's progression. Therefore, antihypertensive medications are typically needed in addition to non-pharmacological therapies to control hypertension in CKD (Peralta *et al*., 2005). However, certain pharmacological treatments have renoprotective and/or cardioprotective effects in addition to their direct blood pressure (BP)-lowering effects; these effects may exist independently of the BP-lowering effects (Slagman *et al*., 2011). Thus, the individual's need for a certain balance of risk reduction should be taken into account when selecting an antihypertensive medication.

To reach BP targets, combination medication therapy is frequently required (Sarafidis *et al*., 2007). Up to 50% of patients with CKD experience volume overload, which is frequently subclinical and a separate risk factor for CVDs (Hung *et al*., 2014). Diuretic therapy has been demonstrated to improve arterial stiffness and left ventricular mass index in patients with CKD and can lessen volume expansion (Edwards *et al.*, 2009; Zamboli *et al*., 2011). Because they have antihypertensive and cardioprotective

properties, diuretics are therefore commonly used in combination medication therapy in CKD (Zamboli *et al*., 2011). Important medications for lowering BP in patients with CKD include thiazide or thiazide-like diuretics (Cirillo *et al*., 2014; Sinha and Agarwal, 2015a). However, little is known about their effectiveness or safety in patients with advanced CKD (Sinha and Agarwal, 2015b).

Thiazide or thiazide-like diuretic monotherapy may play a role in non-proteinuric CKD and should be taken into consideration as a possible first-line therapy (NICE, 2014). Loop diuretics are typically reserved for patients with advanced CKD and cannot be used as first-line antihypertensive therapy like thiazide diuretics. Loop diuretics are helpful, but because of their tubular mechanism of action, which depends primarily on glomerular filtration, larger dosages are frequently needed in patients with lower estimated glomerular filtration rate (eGFR). Given their potent combination, thiazide diuretics and loop diuretics should be used with caution to prevent fluid depletion. In patients with CKD, mineralocorticoid receptor blockers like spironolactone effectively lower BP, but they also increase the risk of hyperkalaemia (Currie *et al*., 2016). These medications may be especially helpful for patients who also have concurrent left ventricular dysfunction because they have been shown to improve systolic and diastolic function in early CKD (Edwards *et al*., 2010).

Despite the diuretics' proven efficacy and safety in the CKD population, there is a dearth of information on their use and effects on BP and renal function among patients with CKD and hypertension in Africa, particularly Nigeria. Therefore, this study sought to determine the prevalence of diuretic use, ascertain their prescribing pattern, and investigate their impact on BP and renal function among patients with CKD and hypertension.

MATERIAL AND METHODS

Study Design, Setting, and Population

This one-year retrospective longitudinal study was carried out in the Nephrology and Cardiology Units of a tertiary hospital in Maiduguri, Nigeria. The study population consists of patients with CKD and hypertension who received care at the study hospital between August 2022 and July 2023.

Sample Size Determination

Based on Yamane's formula (Yamane, 1967), the sample size for the study was determined with a margin of error of 0.05 (e) and a population size of 1000 (N). Therefore, 286 patients were the minimum sample size needed for the study.

Eligibility Criteria

The requirements for inclusion included being 18 years of age or older, having diagnoses of CKD (stages 1–5) and hypertension, and receiving treatment at the study hospital's Nephrology and/or Cardiology Units between August 2022 and July 2023.

Patients' Selection and Data Collection

Using an interval of five, patient's medical files were systematically and randomly chosen. Study data were collected between January 16 and February 15, 2024, using a pretested, predesigned proforma. The names of prescribed antihypertensive medications, creatinine values, and sociodemographic information (age, sex, marital status, religion, and employment status) were extracted from the patient's medical files.

Data Processing and Statistical Analysis

This study used the CKD-EPI Creatinine 2021 Equation to estimate GRF using the National Kidney Foundation calculator. The extracted data from the medical files were first entered into a Microsoft Excel spreadsheet, cleaned, coded, and transferred to Statistical Products and Services Solution (SPSS) version 25 (IBM Corporation) for Windows software for analyses. The study results were presented using descriptive statistics (means and standard deviations, frequencies, and percentages). Within each

group, mean BP, creatinine levels, and eGFR at baseline and three months were compared using the paired-sample-t test, whereas the mean differences of these parameters between two groups were compared using the independent samples-t test at the $P < 0.05$ statistically significant level.

RESULTS

Baseline Characteristics of the Study Population

Most patients (63.7%) are males, whereas the average age of the study population was 54.5 ± 13.2 years. The majority of patients (29.0%) were between 45 and 54 years old, married (82.6%), and of Islamic faith (79.3%) (Table 1). The baseline mean BP was 172/103 mmHg, while the mean creatinine level was 866.2 µmol/L. An overwhelming majority of patients (91.7%) were in CKD stage 5 (Table 2).

The Prevalence of Diuretic Use, and Prescribing Patterns of Diuretics and Other Antihypertensive Medications

A high prevalence of diuretic use (80.3%) was observed in the study (Figure 1). Loop diuretics ranked highest (97.6%) among diuretic types prescribed, while the analysis of individual diuretics revealed furosemide (77.8%) as the most frequently prescribed. Also, worthy to note is the abysmal low utilization of thiazides in the study population (0.4%) (Figure 2). The analysis of other prescribed antihypertensive medications showed losartan (29.4%) followed by nifedipine (24.7%) as the most commonly prescribed (Figure 3).

Table 1: Baseline Characteristics of the Study Population

Variables	n (%)
Sex	
Female	191(63.7)
Male	109 (36.3)
Age Groups (Years)	
20-34	15 (5.0)
35-44	52 (17.3)
45-54	87 (29.0)
55-64	83 (27.7)
≥ 65	63 (21.0)
Marital Status	
Widowed	24 (8.0)
Single	17 (5.7)
Divorced	11(3.7)
Married	248 (82.6)
Occupation	
None	24 (8.0)
House wife	95 (31.7)
Retired	48 (16.0)
Civil servant	63 (21.0)
Business	70 (23.3)
Religion	
Christianity	62 (20.7)
Islam	238 (79.3)

Table 2: Baseline Clinical and Biochemical Parameters

Variables	Mean ± SD or n (%)
SBP (mmHg)	172.3 ± 18.6
DBP (mmHg)	103.1 ± 10.2
Creatinine (µmol/L)	866.2 ± 402.6
eGFR (mL/min/1.73m^2)	7.1 ± 6.9
CKD Stages	
1	0 (0.0)
2	1 (0.3)
3	2 (0.7)
4	22 (7.3)
5	275 (91.7)

CKD: chronic kidney disease, DBP: diastolic blood pressure, SBP: systolic blood pressure, eGFR: estimated glomerular filtration rate

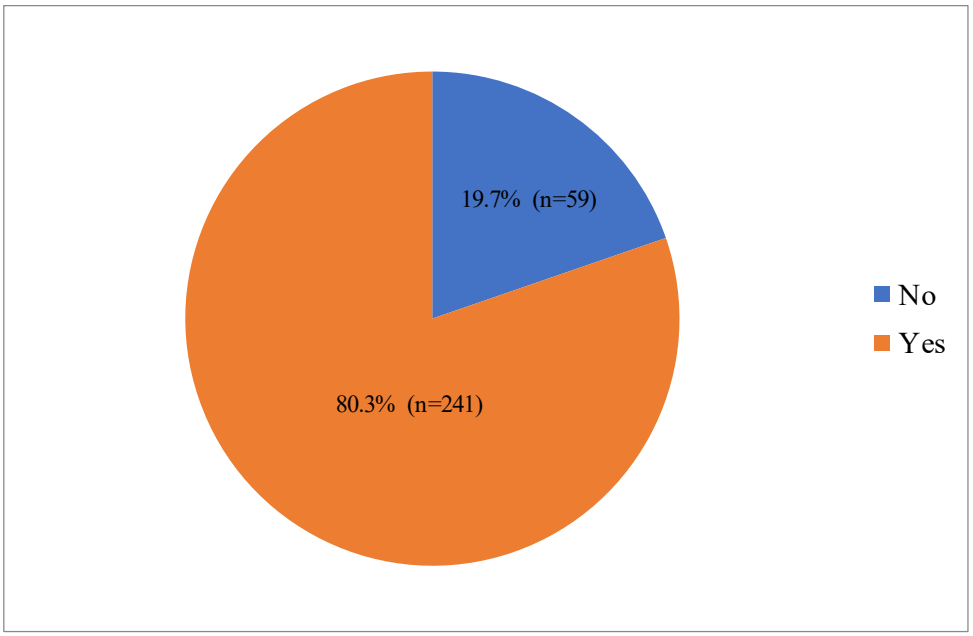

Figure 1: The Prevalence of Diuretic Prescriptions in the Study Population

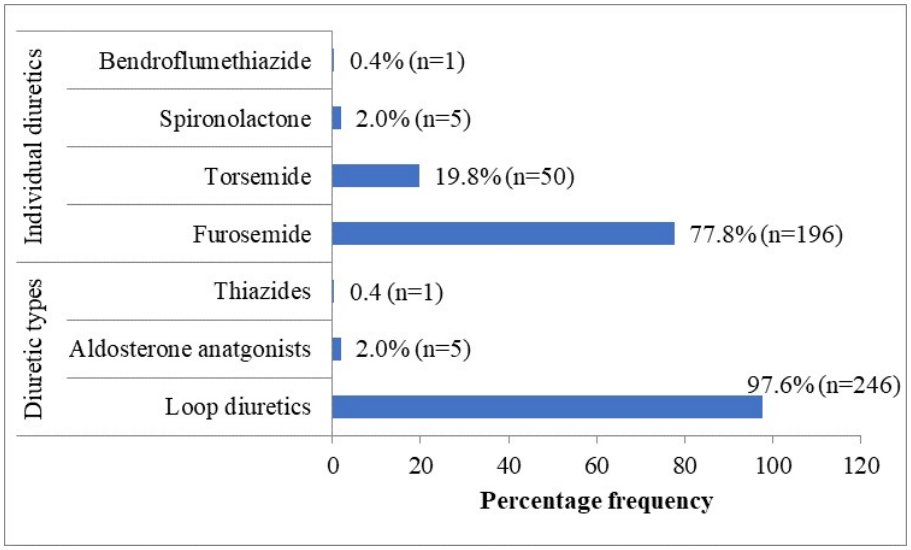

Figure 2: The Prescribing Pattern of Diuretics

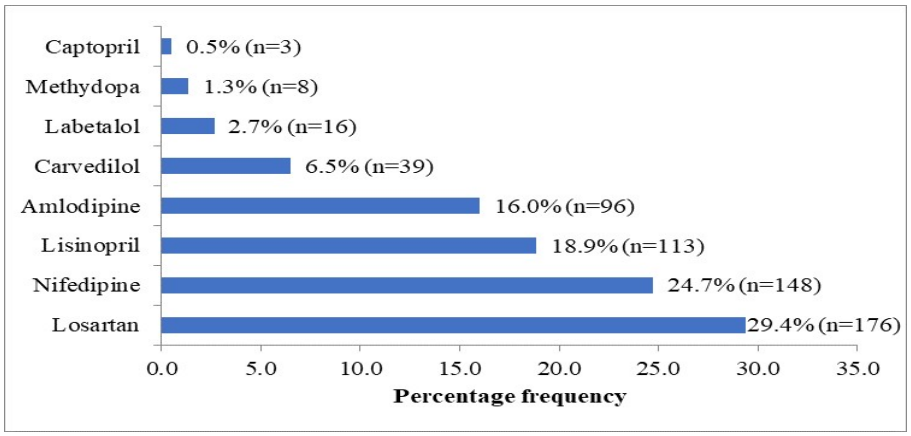

Figure 3: The Prescribing Patterns of Other Antihypertensive Medications

Impact of Diuretic Use on Blood Pressure and Renal Function

Patients who had at least one diuretic in their prescriptions achieved significantly high SBP (32.3 mmHg) and DBP (12.8 mmHg) reductions at 3 months, respectively. Also, the group that had at least one diuretic agent in addition to other antihypertensive medications achieved a significantly high reduction and increase in creatinine level (180 µmol/L) and eGFR (1.7 mL/min/1.73m^2) at 3 months, respectively (Table 2). On comparison of the two groups, it was observed that the mean reduction in the creatinine value was significantly much higher in the group that received diuretics than in the group that did not (180 µmol/L versus 30 µmol/L, P=0.001). Also, greater improvement in eGFR was recorded in the diuretic group compared to the group that did not use diuretics, though no statistically significant level was reached (1.7 mL/min/1.73m^2 versus 1.2 mL/min/1.73m^2, P=0.394) (Table 2).

DISCUSSION

The present study found that an overwhelming proportion of the study population was prescribed diuretics with furosemide as the most commonly prescribed. Also, it was observed that the inclusion of diuretics led to an improved BP, creatinine level, and eGFR in the study population. Utilization of loop diuretics was very high in the study population. An overwhelming proportion of patients with advanced-stage CKD could be responsible for the very high use of loop diuretics. Consistent with previous hospital-based studies, a high prevalence of advanced-stage CKD is common in Nigeria (Ulasi and Ijoma, 2010; Okoro and Farate, 2019), probably due to late presentation to the hospitals. This suggests that loop diuretics were prescribed mainly to reduce extracellular fluid volume overload oblivious of their antihypertensive effects (Fitzpatrick *et al*., 2022). Worthy to note is the very low utilization of thiazide or thiazide-like diuretics in the study population. This finding suggests that physicians at the study hospital still hold on to the general concept/old belief or guideline recommendations that thiazide and thiazide-like diuretics are ineffective, especially in advanced-stage CKD and should be avoided in patients with an eGFR < 30 mL/min/1.73 m^2 (K/DOQI, 2004; Chobanian *et al*., 2003) or < 45 mL/min/1.73 m^2 (Williams *et al*., 2018), giving preference to loop diuretics. Contrary to this concept and guidelines, available evidence has demonstrated the effectiveness of thiazide and thiazide-like diuretics in improving BP in advanced-stage CKD (Dussol *et al*., 2005; Dussol *et al*., 2012; Agarwal *et al*., 2014; Agarwal *et al*., 2021). Apart from the effectiveness of thiazides and thiazide-like diuretics in reducing BP in the CKD population, their safety in this vulnerable population has been demonstrated in previous studies (ALLHAT, 2002; Vogt *et al*., 2008; Barzilay *et al*., 2012). Because of this, there is an urgent need for regular retraining of

physicians caring for these patients at the study hospital to be abreast with the global best practices in the management of hypertension in CKD. This will help to improve the quality of care offered to this vulnerable population.

Table 2: Impact of Diuretics on Blood Pressure and Renal Function

Variables	Diuretic use	Baseline Mean ± SD	3-months Mean ± SD	Diff.	P value	Diff. in diff.	P value
SBP (mmHg)							
	Yes	174.2 ± 18.2	141.9 ± 12.7	-32.3	<0.001*	-3.9	0.131
	No	164.4 ± 18.4	135.9 ± 13.4	-28.4	<0.001*		
DBP (mmHg)							
	Yes	103.8 ± 9.7	91.0 ± 8.7	-12.8	<0.001*	-0.8	0.609
	No	100.4 ± 11.9	88.4 ± 10.1	-12.0	<0.001*		
Creatinine (μmol/L)							
	Yes	908.8 ± 400.6	728.8 ± 304.3	-180	<0.001*	-150.0	0.001**
	No	692.4 ± 364.8	662.4 ± 379.7	-30	0.529		
eGFR (mL/min/1.73 m^2)							
	Yes	6.2 ± 4.7	7.9 ± 6.0	1.7	<0.001*	0.5	0.394
	No	10.6 ± 11.7	11.8 ± 14.3	1.2	0.121		

*SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; SD: standard deviation; *Paired sample-t test significant at p<0.05; **Independent samples-t test significant at p<0.05*
Note: Diff (difference) = 3-months minus baseline, Diff. in diff. = difference (non-diuretic group) minus difference (diuretic group)

In the present study, the inclusion of diuretics in the antihypertensive therapy led to improvement in BP at three months. This result is consistent with evidence that salt and water retention play a major role to the development of hypertension in these patients (Agarwal *et al*., 2014; Agarwal *et al*., 2021). Also, inclusion of diuretics in the antihypertensive therapy significantly decreased creatinine level and increased the eGFR, respectively. Although diuretics' direct benefit on renal function is still debatable, their potential to reduce BP and potentiate the effects of renin-angiotensin-aldosterone system (RAAS) blockade by increasing intraglomerular pressure's renin-angiotensin system dependence may account for their renoprotective effects. Nevertheless, other possible mechanisms independent of these parameters warrant investigation in future studies.

Strength and Limitations

To our knowledge, this is the first study investigating the impact of diuretics on BP, and renal function in the CKD population in Africa. Therefore, the findings of this study can stimulate other African researchers to

conduct a randomized clinical trial on this topic.

The study had some limitations. First, the small sample size, the use of only one hospital, and short follow-up duration could limit the generalization of the study findings. Secondly, even though the use of patients' medical records to extract prescribed medications eliminated recall bias, though exposure bias may persist. This might occur if the recommended medications were not taken. Therefore, findings must be interpreted cautiously, while robust, large, and multi-centered randomized controlled clinical trials in various African countries are warranted.

CONCLUSION

A significant proportion of the study population was prescribed diuretics mainly furosemide with or without other antihypertensive medications. Also, this study demonstrates that the addition of diuretics to antihypertensive regimen of patients with advanced CKD can impact BP, and renal function positively. Therefore, a more robust studies, such as case-control studies are recommended to confirm the findings of the present study.

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