



## ANTIHYPERTENSIVE COMBINATIONS FOR ACHIEVING GOAL BLOOD PRESSURE USING THE JOINT NATIONAL COMMITTEE (JNC) 7 GUIDELINE IN A NIGERIA TEACHING HOSPITAL

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### ABSTRACT

The Joint National Committee (JNC7) guideline recommends a combination of antihypertensive medications for achieving target blood pressure. The objective of this study was to evaluate antihypertensive combinations and target blood pressure (BP) goals using JNC7 guidelines in patients with hypertension. A retrospective study was carried out among 679 patients treated for hypertension between 2004 and 2012 in the University of Nigeria Teaching Hospital Ituku-Ozalla Enugu State. Sociodemographic details, medication and clinical data were collected from 201 patients whose medical record met the eligibility criteria. Data were analyzed using both descriptive and inferential statistics. The association between use of antihypertensive combination and achieving BP control was tested with Chi-Square and results presented in frequencies and percentages. Logistic regression was used to predict BP control. P-value < 0.05 was considered significant. The result indicated that most of the patients were women 276 (55.0%) and within the age group of 50-55 years. More than half 294 (58.8%) of the prescriptions were two drug-combinations. A combination of Angiotensin Converting Enzyme Inhibitors (ACEI) and Calcium Channel Blockers (CCB) with thiazide diuretics was mostly prescribed for more than two drug combinations. Forty-three percent cases of stage 1 hypertension were treated with two drug-combinations whereas 111 (22.2%) of stage 2 hypertension cases were managed with more than two drug-combinations. The overall BP goal achieved was 249 (49.8%). Thirty-five percent of the BP goal achieved was attributed to two drug-combinations. In conclusion, more patients received two drug combinations compared to more than two drug combination and two drug combinations were more effective in achieving goal BP.

**KEYWORDS:** Hypertension, Antihypertensive combinations, JNC7, BP control.

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### INTRODUCTION

Hypertension has emerged as a global health problem and the global prevalence of the disease was at 40% in 2011 [1,2]. It is estimated that by 2025, 125.5 million people will be living with hypertension in sub-Saharan Africa [3]. Although preventable, it remains the leading risk factor for heart disease, stroke and a major cause of morbidity and mortality worldwide [4]. A systematic study documented the overall crude prevalence of hypertension among Nigerian adults to be between the ranges of 2.1% to 47.2% [5]. The World Health Organization (WHO) estimated that cardiovascular diseases were

responsible for 36.5% of deaths due to non-communicable diseases (NCDs) in Nigeria in 2016 [6].

Several antihypertensive therapies are available and useful in lowering blood pressure and minimizing the morbidity and mortality associated with hypertension. The combination of antihypertensive drugs has been promoted and endorsed by treatment guidelines. The European guideline recommends a combination of antihypertensive agents in patients with high cardiovascular risk [7]. The Joint National Committee on Prevention, Detection, Evaluation, and treatment of High Blood

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Pressure (JNC7) reaffirms the appropriate combination of the antihypertensive drug as a tool for effective BP control, since in most patients BP cannot be controlled with one drug alone [8]. The JNC7 guideline classified hypertension into stages and recommended thiazide diuretic (TD) in combination with drugs from the other four antihypertensive drug classes (calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers) as appropriate for initiating and continuing therapy in hypertensive patients. The JNC 7 guideline was used as a reference document due to her popularity at the time of the study and the strong recommendation for antihypertensive combination therapies in the management of hypertension with or without comorbidities.

A number of drug utilization studies on antihypertensive drugs in Nigeria have reported that drug combinations were more commonly used than monotherapy [9-13]. Despite the availability of guidelines and the use of antihypertensive drug combinations, hypertension is still poorly controlled in sub-Saharan Africa (SSA) [14]. Stroke a major outcome of uncontrolled hypertension has increased by 46% since 1990 to become the fifth leading cause of death in SSA [15]. In Nigeria, three different studies reported the proportion of patients with controlled BP lower than 140/90 mmHg to be 30.5%, 9.0%, and 32.9% [12, 16, 17].

The poor prognosis of hypertension in Nigeria has been attributed to patient factors, poor adherence to medicine, financial constraints, high pill burden [17], and poor access to hospital [18]. However, it is not yet clear how the use of antihypertensive combination recommended by JNC 7 affects BP control. Hence the purpose of this study was to describe the use of antihypertensive combinations for achieving goal blood pressure (<140/90 mmHg and 130/80mmHg for Diabetic Mellitus (DM) and Chronic Kidney Disease (CKD) patients) using the JNC 7 guideline in a Nigeria teaching hospital.

## **METHODS**

### **Study design**

This study was a retrospective study of 679 hypertensive patients folders carried out from December 2013 to February 2014. Two hundred and one (201) patient folders that met the eligibility criteria were included in the analysis.

### **Study setting**

The study was carried out at the University of Nigeria Teaching Hospital (UNTH) Ituku-Ozalla Enugu

State. The hypertensive patients in this tertiary hospital are seen by consultants (cardiologists, family physicians), resident doctors and house officers. The hospital is a referral centre that is well equipped for research and specialist training programmes.

### **Study population**

The folders of hypertensive patients seen in the outpatient from 2004-2012 were retrieved from the outpatient medical records for the study. The eligibility criteria were adults above 18years diagnosed of essential hypertension, treatment with two or more antihypertensive combinations recommended by JNC for not less than 3 months, presence of thiazide diuretics in the prescription, patients that kept at least 3 consecutive appointments in one year and documentation of BP in each visit. The study excluded records of pregnant patients, patients with severe degenerative diseases and folders with confusing information.

### **Ethical clearance**

The study protocol was approved by the ethical committee of the UNTH Enugu with the number NHREC/05/01200B – FWA00002458 --- IRB00002323.

### **Data extraction**

Six hundred and seventy-nine (679) hypertensive patient folders were available in the outpatient medical record, 524 received prescriptions of antihypertensive combinations, two hundred and one (201) records met the eligibility criteria and data were collected from them using a proforma. Data were extracted according to the encounters the patients had with the antihypertensive combinations. A patient can have an encounter with not less than two antihypertensive combinations recommended by JNC 7. An encounter starts from when two or more than two antihypertensive combinations under investigation are prescribed and terminates when the patient is switched to another antihypertensive combination. The pretreatment BP was the blood pressure at which the patient commenced the treatment combination and was used to classify the patient into hypertension stage 1 or stage 2 according to JNC7 classification [8]. The mean of the last two documented blood pressure was used to determine if the blood pressure was controlled or not controlled. The patients had a total of 500 encounters. Three types of data were extracted from the patients' records: demographic data (sex, age, social habits, and occupation), medication data (antihypertensive drug combination and treatment

year) and clinical data (stage of hypertension, blood pressure, and comorbidities). Antihypertensive drugs with two active ingredients except for thiazide diuretic were regarded as a combination therapy.

### Data analysis

Data were coded into IBM SPSS version 21 and analyzed using descriptive and inferential statistics. The results are presented as frequencies, percentages and odd ratios. Association between drug combinations, stage of hypertension, comorbidities and BP control was tested with Chi-Square. A controlled BP was defined as a BP of <140/90 mmHg and 130/80mmHg for Diabetic Mellitus (DM) and Chronic Kidney Disease (CKD) patients [8]. Logistic regression was used to predict BP control. Controlled BP was coded 1 and poorly controlled BP coded as zero. The predicting variables were drug combination, stage of hypertension and comorbidities. The level of significance was set at  $P < 0.05$ .

### RESULTS

In Table 1, the demographic characteristics of the patients showed that 276 (55.2%) of the encounters were made by females and most of them were within the age group of 50-59 years. In terms of occupations, 140 (28.1%) were civil servants.

The total number of antihypertensive prescribed was 1950 with a mean of 3.9. Patients made a total of 294 (58.8%) encounters with two drug combinations. Considering two drug combinations, the drug class mostly prescribed with a thiazide diuretic, was Angiotensin Converting Enzyme Inhibitors (ACEI) 324 (68.6%), followed by Calcium Channel Blockers (CCB) 213 (43.6%). For more than two drug combinations, ACEIs and CCBs 136 (27.2%) were the most frequently prescribed followed by Angiotensin Receptor Blockers (ARBs) and CCBs 56 (11%) (Table 2).

Angiotensin Converting Enzyme Inhibitors were the drug class mostly prescribed for co-morbidity while Beta Blockers (BB) were the least prescribed (Table 3). ACEI were prescribed for 63 (64.9%) of the diabetic patient and 17 (85.9%) of hypertensive heart disease patient.

The use of the antihypertensive combinations recommended by JNC 7 increased with year. The highest number of encounters was seen in 2012, 79 (26.6%) and 63 (31.0%) for two drug combinations and more than two drug combinations respectively (Figure 1).

The documented blood pressure showed that nearly two-thirds of the patients 312 (62.4%) had stage 1 hypertension at the initiation of treatment, of which 217 (43.4%) used two drug combinations and 95 (19.0%) more than 2 drug combinations. More than half of the patient 260 (52.0%) had co-morbidity and used 150 (57.7%) of two drug combinations. Major co-morbidities seen were Diabetes Mellitus (DM) 97 (37.3%) and Heart Failure (HF) 65 (25%). The mean pretreatment systolic blood pressure was  $138.49 \pm 18.09$  and  $154.08 \pm 23.08$  for two drug combinations and more than two drug combinations respectively (Table 4). The overall BP controlled was 249 (49.8%) with 176 (34.6%) of the controlled BP attributed to two-drug combinations. More stage 1 hypertension 195 (39.0%) achieved controlled BP compared to stage 2 hypertension 54 (10.8%). A higher percentage of diabetic 72 (14.4%) and CKD 6 (1.2%) patients did not achieve goal BP while more patients without comorbidity 130 (26.0%) achieved goal BP (Table 5).

Comorbidity, stage of hypertension, and drug combinations predicted the control of blood pressure (Table 6). The odds of BP control is increased by 1.425 for stage 2 hypertension, 0.518 for every unit increase in the number of combination and decreased by 0.771 for chronic kidney diseases.

### DISCUSSION

The prescription pattern observed in this study shows that either two or more than two antihypertensive drug combinations were used for treatment at any stage of hypertension and two drug combinations were more prescribed. The drug class mostly prescribed with thiazide diuretic was ACEI while BB was the least. Approximately all patients with diabetes, heart failure, chronic kidney disease received a combination that included an ACEI or ARB. In contrast, most patients with heart failure did not receive a prescription of BB even though beta1 selective blockers have been recommended to be beneficial to heart failure patients. Patients with heart failure and history of stroke received a combination that included CCB which is not recommended for these patients. Most patients were at stage 1 hypertension and have associated comorbidities. A little less than half of the patients achieved goal blood pressure. More patients with co-morbidities did not achieve goal blood pressure. Hypertension stage, comorbidity and number of antihypertensive agents predicted

**Table 1: Sociodemographic characters of patient**

<b>Variables</b>	<b>Frequency (%)</b>
<b>Gender</b>	
Females	276(55.2)
Males	224(44.8)
<b>Age</b>	
30-39	7(1.4)
40-49	54(10.8)
50-59	163(32.6)
60-69	150(30.0)
70-79	105(21.0)
80-89	21(4.2)
<b>Occupation</b>	
Civil servants	140 (28.1)
Artisan	82 (16.40)
Unemployed	94 (18.8)
Trader	84 (16.8)
Retired	99 (19.8)
<b>Social habit</b>	
Alcohol	73 (14.4)
Cigarette	10 (2.0)
Alcohol and cigarette	71 (14.0)
None	356 (69.7)

**Table 2: Prescription pattern of antihypertensive combinations.**

<b>Variable</b>	<b>Frequency (%)</b>
Two drug combinations	294 (58.8)
> Two drug combinations	206 (41.2)
<b>Two drug combination</b>	
TD + ACEI	324 (68.6)
TD + CCB	213 (43.6)
TD+ARB	116 (23.2)
TD+BB	40 (8.0)
<b>&gt; Two drug combinations</b>	
TD+ACEI+CCB	136 (27.2)
TD+ARB+CCB	56 (11.0)
TD+ACEI+BB	20 (4.0)
TD+BB+CCB	19 (3.8)
TD+ACEI+CCB+BB	12 (2.4)
TD+ARB+BB	10 (2.0)
TD+CCB+BB+ARB	4 (0.8)

TD=Thiazide Diuretic, ACEI=Angiotensin Converting Enzyme Inhibitor, ARB= Angiotensin Receptor Blocker, BB= Beta Blocker, CCB=Calcium Channel Blocker.

**Table 3: Specific drug class prescribed for comorbid patients**

Co morbidity	ACEI	CCB	ARB	BB
	n(%)	n (%)	n (%)	n (%)
Cardiovascular accident (CVA) (33)	27 (81.8)	11 (33.3)	4 (12.1)	4 (12.1)
Heart failure (65)	49 (75.4)	15 (23.1)	14 (21.5)	3 (4.6)
Diabetes mellitus (DM) (97)	63 (64.9)	50 (51.5)	32 (33)	6 (6.2)
Chronic kidney disease (11)	10 (90.9)	3 (27.3)	1 (9.1)	2 (18.2)
(HHD & DM) (19)	17 (85.9)	11 (57.9)	2 (10.50)	---
Hypertensive Heart disease (HHD) (35)	23 (65.7)	15 (42.9)	6 (17.1)	3 (8.6)
No comorbidity (240)	154 (64.2)	113 (47.1)	57 (23.8)	22 (9.2)
P-value	0.037	0.004	0.08	0.438

ACEI= Angiotensin Converting Enzyme Inhibitor, ARB= Angiotensin Receptor Blocker, BB= Beta Blocker, CCB=Calcium Channel Blocker, n= Number of patients.

**Table 4: Clinical data by drug combination**

Variables	2 drug combination Frequency (%)	>2 drug combination Frequency (%)	Total Frequency (%)	P value
<b>Stage of hypertension</b>				<0.001*
Stage 1	217 (43.4)	95 (19.0)	312 (62.4)	
Stage 2	77 (15.4)	111(22.2)	188 (37.6)	
<b>Comorbidity</b>				0.02*
Cardiovascular accident	21 (8.1)	12 (4.6)	33 (12.7)	
Heart failure	51 (19.6)	14 (5.4)	65 (25)	
Diabetes mellitus (DM)	47 (18.1)	50 (19.2)	97 (37.3)	
Chronic kidney disease	6 (2.3)	5 (1.9)	11 (4.2)	
Hypertensive Heart Disease	18 (6.9)	17 (6.5)	35 (13.5)	
HHD & DM	7 (2.7)	12 (4.6)	19 (7.3)	
Total	150 (57.7)	110 (42.3)	260 (100)	
<b>BP Mean (<math>\pm</math>sd)</b>				
First systolic blood pressure	138.49 $\pm$ (18.09)	154.08 $\pm$ (23.08)		
Final systolic blood pressure	84.79 $\pm$ (11.68)	91.86 $\pm$ (13.83)		
First diastolic blood pressure	132.18 $\pm$ (18.01)	141.37 $\pm$ (20.01)		
Final diastolic blood pressure	81.01 $\pm$ (11.82)	84.85(12.53)		

\*P <0.05, BP= blood pressure.

**Table 5: Percentage blood pressure control by drug combination, stage, and comorbidity**

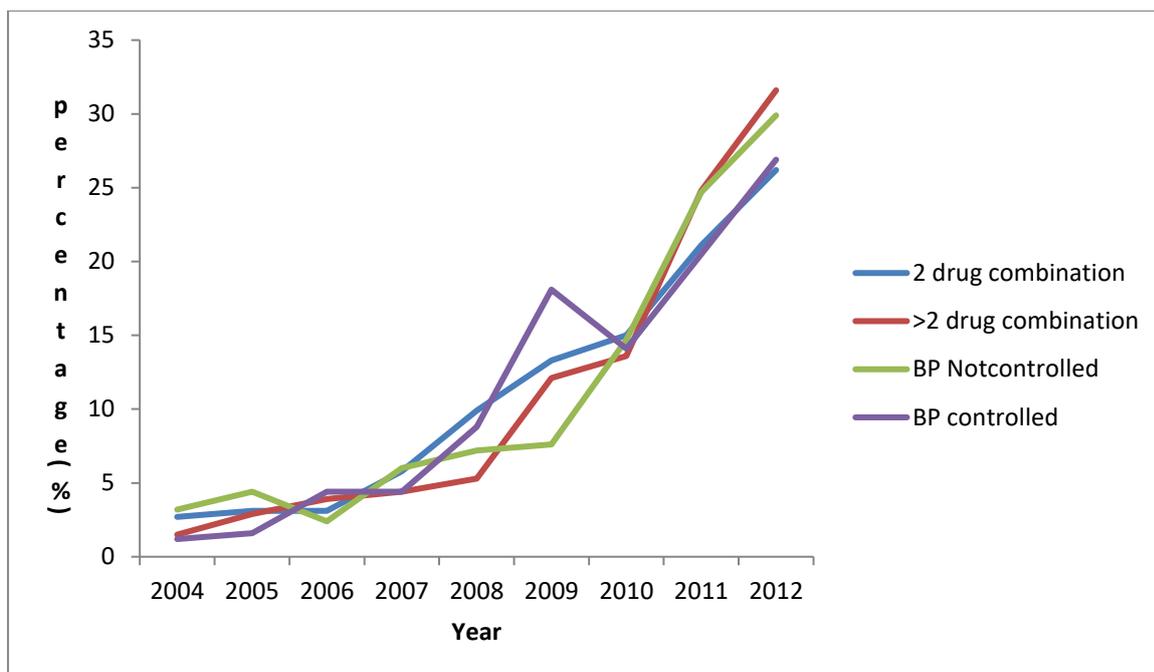
	Controlled n (%)	Not controlled n (%)	Total n (%)	P value
<b>Drug combination</b>				<0.001*
2 drug combination	173 (34.6)	121 (24.2)	294 (58.8)	
>2 drug combination	76 (15.2)	130 (26.0)	206 (41.2)	
Total	249 (49.8)	251 (50.2)	500(100)	
<b>Stage of hypertension</b>				
Stage 1	195 (39.0)	117 (23.4)	312 (62.4)	<0.001*
Stage 2	54 (10.8)	134 (26.8)	188 (37.6)	
Total	249 (49.8)	251 (50.2)	500 (100)	
<b>Co-morbidity</b>				
Cardiovascular accident	19 (3.8)	14 (2.8)	33 (6.6)	<0.001*
Heart failure	37 (7.4)	28 (5.6)	65 (13)	
Diabetes mellitus (DM)	25 (5.0)	72 (14.4)	97 (19.4)	
Chronic kidney disease	5 (1.0)	6 (1.2)	11 (2.2)	
Hypertensive Heart Disease	25 (5.0)	10 (2.0)	35 (7.0)	
HHD & DM	8 (1.6)	11 (2.2)	19(3.8)	
No co-morbidity	130 (26.0)	110 (22)	240 (48)	
<b>Total</b>	249 (49.8)	251 (50.2)	500 (100)	

\*P <0.05, n=number of patients

**Table 6: Logistic regression predicting blood pressure control**

	B	S.E	Sig	Exp (95% Confidence Interval)
Stage 2 hypertension	1.425	.217	<.001*	4.159 (2.717 – 6.365)
Cardiovascular accident (CVA)	-.771	.423	.068	.462 (.202 – 1.059)
Heart Failure	-.392	.554	.480	.676 (.228 – 2.003)
Diabetes Mellitus (DM)	-.687	.486	.157	.503 (.194 – 1.303)
Chronic Kidney Disease	-2.122	.468	<.001*	.120 (.048 -- .300)
CVA & DM	-.992	.749	.185	.371 (.085 – 1.609)
Hypertensive heart disease	-1.116	.634	.078	.328 (.094 – 1.136)
>Two drug Combination	.518	.211	.014*	1.679 (1.109 – 2.540)
Constant	-.270	.424	.525	.764

\*P<0.001



**Figure 1: Trend in use of drug combination and blood pressure control.**

BP control. The number of encounters with antihypertensive increased with year.

The higher proportion of two antihypertensive combinations prescribed might be due to the majority of the patients being at stage 1 hypertension. Also, by the stepwise approach recommended by JNC 7 in the use of multiple antihypertensive drugs, only patients who did not attain goal BP on two drug combinations will receive additional therapy. Other studies in Nigeria [9,12] also documented two antihypertensive combinations as the most prescribed antihypertensive combinations. ACEI was the drug class mostly prescribed with TD in the presence or absence of compelling indications even though it is documented to have low efficacy on black patients. This is possibly due to the physician's choice or demonstrated benefits of ACEI for all compelling indications. Again, ACEI produces better BP control when used in combination with diuretics [19]. The choice of combination of diuretic and ACEI as the most prescribed two drug combinations is consistent with Nigerian reports [11, 12]. However, another study in Nigeria documented CCB and diuretics as the most prescribed two antihypertensive combinations [13]. The similarities and differences could be the physician's choice as all the studies were done in tertiary institutions. For more than two drug combinations, the drug classes mostly prescribed with TD were ACEI and CCB which conforms to a Nigerian study [9]. This is

probably due to the availability of the drugs in the hospital and the environment. Combinations that include BB were the least prescribed two antihypertensive combinations while CCB, ARB and BB with TD were least prescribed more than two drug combinations. This is probably due to the risk of bradycardia with CCB and BB combinations [8]. The ARB is also known to be at the high cost.

Most diabetic and CKD patients received either a prescription of ACEI or ARB. This is likely due to the recommendation of these classes of drugs for the comorbidities [8]. This suggests that co-morbidity was considered while making prescriptions. Surprisingly, most heart failure patients did not receive a BB. It might be because of the age and the race of the people in the present study as BB is documented to be more effective in the young and white race [8]. A combination that included a CCB was prescribed for heart failure and stroke patients. Their use might be due to the documented benefits of CCB for black hypertensive patients.

More patients were at stage 1 hypertension at the first visit which contrasts the reports of two Nigeria studies that reported a higher proportion of patients to be at stage 2 hypertension on their first visit [10,11]. The difference is likely due to the population selected for this present study, as only patients that keep to doctor's appointments which might suggest adherence to treatment were selected. However, a study in South India reported (4.3%) of

prehypertension, (68.1%) of stage 1 hypertension and (27.6%) of stage 2 hypertension [21]. The high percentage of comorbidities documented in this study is in line with existing evidence of higher incidence of concurrent diseases such as left ventricular hypertrophy, cardiac failure, diabetes mellitus and chronic renal failure among black hypertensive patients [20]. Diabetes being the highest comorbidity conforms to other studies in Nigerian [11] and Malaysia [22] and this can be explained by diabetes being a known risk factor for hypertension.

The BP goal achieved in this study is higher than other reports that used the same BP goal of <140/90mmHg in Nigeria 32.9% [17], 30.5% [12] and 9% [16]. The difference in the control rate is most likely due to the selection of the population in this present study. The population in this study is being managed with antihypertensive combinations recommended by the JNC7 guideline in a tertiary health center. Also, our study was done in urban areas inhabited majorly by civil servants and retirees who might have a better knowledge of the consequences of uncontrolled BP. However, the goal BP achieved in this study is consistent with the value (45.6%) reported in the United States [23] that evaluated adherence to JNC7. This brings to light the importance of periodic consultations with healthcare providers and following guidelines in the management of chronic diseases. More patients achieved goal BP with two drug combinations irrespective of the stage of hypertension. This is almost in line with the Hypertension Optimal Treatment Study (HOTS), where only (23%) of the patient needed more than two drug combinations to achieve their goal BP [24]. However, Calhoun *et al* [25] reported that triple drug combination achieved goal systolic BP more than two drug combinations. The difference might be in the class of antihypertensive drugs included in our study and also our study considered co-morbid conditions existing among patients in the report of BP control. Also, patients were managed with a stepwise approach which implies that only those not controlled on two drugs will receive a higher number of drugs. More patients at stage 1 hypertension achieved goal BP compared to patients at stage 2. This can be attributed to stage 1 BP cut point being lower than stage 2 which makes it easier for the goal BP to be attained. The logistic regression showed that stage 2 patients and more than two drug combinations increase the odds of BP controls. This is probably due to interactions with other factors that affect BP control. It might suggest that some stage 2 patients need additional drugs to reach goal BP. There was

difficulty in achieving goal BP in patients with CKD. This is probably due to the known interconnection between BP and CKD. Elevation of BP deteriorates renal function and a decline in renal function sustains high BP [8]. Also, CKD is known to cause resistance to antihypertensive therapy [26]. The study also noted that approximately a quarter of patients with diabetes achieved goal BP despite the use of thiazide diuretics and ACEI. This finding is consistent with the result of a US-based study [23]. It can be attributed to the lower BP point needed for diabetic hypertensive patients to be marked controlled. It means that there is a need to intensify treatment in diabetic patients with hypertension.

Our report showed that patients had more encounters with antihypertensive as the year progresses, this might be because more patients were enrolled for treatment and also increased acceptance of JNC 7 recommendation by health practitioners. This coincides with a Cantona Sarajevo [27] report on the utilization of antihypertensive.

The study was limited by its retrospective nature, and could not evaluate if patients were advised on lifestyle modification which can affect BP control. The study did not assess laboratory tests order and results for the patients as they can influence prescription. The study measured adherence to treatment with patients' ability to meet up with hospital appointments which might not be accurate. This study makes a novel contribution in that it is the first to study the prescription of antihypertensive combinations alone and goal BP achieved according to the recommendation of JNC 7 in a teaching hospital in Southeast Nigeria. The JNC 7 document was used because of its popularity when this study was carried out and the years covered by the study. Notwithstanding the limitations, the study has shown a direction in the use of antihypertensive combinations in the teaching hospital.

## CONCLUSIONS

This study showed that two drug combinations are used more frequently in the treatment of hypertension, and ACEI was the drug class most commonly prescribed with thiazide diuretics. Two drug combinations were more effective in achieving goal BP. This suggests that there is a need to carefully select patients that will need more than two drug combinations for optimal control of BP. This shows that physicians adhere to the JNC7 recommendation of a stepwise approach to the management of hypertension. There is an increase

in the rate of BP control when treatment guidelines are adhered to.

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