



Original Research Article

Comparison of the Long-Term Efficacy and Some Metabolic Effects of Initiating Therapy with Amlodipine or Hydrochlorothiazide in Hypertensive Type 2 Diabetic Nigerians

Iyalomhe GBS¹, Omogbai EKI², Isah AO³, Iyalomhe SI⁴, Okhiai O⁵, Dada FL⁶, Iyalomhe OOB⁷

¹Associate Professor & Head, Department of Pharmacology and Therapeutics, College of Medicine, Ambrose Alli University, Ekpoma, Nigeria

²Professor, Dept. of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

³Professor, Department of Internal Medicine, College of Medical Sciences, University of Benin, Benin City, Nigeria

⁴Chief Matron, Department of Public Health and Primary Health Care, Central Hospital, Auchi, Nigeria

⁵Senior Lecturer & Head, Dept. of Nursing Sciences, College of Medicine, Ambrose Alli University, Ekpoma.

⁶Head, Department of Laboratory Services, Irrua Specialist Teaching Hospital, Irrua, Nigeria

⁷Research Fellow, Department of Physiology, School of Medicine, Johns Hopkins University, Baltimore, MD 21205, USA

Corresponding Author: Iyalomhe GBS

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ABSTRACT

Background: It is not well investigated whether calcium channel blockers (CCBs) are superior to the recommended low dose thiazide diuretics for initiating therapy in black hypertensive patients with type 2 diabetes mellitus (DM).

Aim: To determine whether amlodipine (AML) or hydrochlorothiazide (HCZ) would be preferable to initiate treatment in hypertensive diabetic Nigerians.

Materials and Methods: Forty newly diagnosed hypertensive Nigerians with controlled type 2 DM aged 43-68 years having blood pressure (BP) >150/90 and ≤ 180/120 mmHg, were recruited into a randomized, open-label, prospective, two-centre study. The diabetics were randomly allocated into AML and HCZ groups. Each group comprised 20 (10 males (M) + 10 females (F)) and they received therapy, respectively, with AML 10mg and HCZ 25 mg for 48 weeks. Body mass index (BMI), BP, heart rate (HR), 24h urine volume, urine glucose and albumin concentration were assessed at baseline and at the end of weeks 1, 3, 6, 12, 24, 36 and 48. The primary efficacy variables were reduction in mean trough sitting diastolic BP (DBP) and systolic BP (SBP), such that BP < 130/80 mmHg was regarded as normalised. Data were analysed using Proc ANOVA and Duncan Multiple Range Test (SAS, 2004) and significance was set at P < 0.05.

Results: In AML group at week 12, 5 patients vs 4 patients in HCZ group, had DBP < 90 mmHg (25% vs 20%; P < 0.01). No patient had BP < 130/80 mmHg. At week 48, 6 patients in AML group and 4 in HCZ group had BP < 130/80 mmHg (30% vs 20%; P < 0.01). At week 48, mean M vs F % decrease in urine glucose concentration was 8.1/8.2 in AML group and increase of 2.7/2.1 in HCZ group (P < 0.005), respectively. M and F decrease in baseline urine albumin concentration was 9.0 vs 12.0 and 16.0 vs 12.0 mg/dl in AML and HCZ groups (P < 0.0003), respectively.

Conclusion: This study demonstrates that, by initiating antihypertensive therapy with AML or HCZ in type 2 diabetic Nigerians, there are greater reductions in BP with AML in comparison to HCZ. AML has a more beneficial effect over HCZ on urine glucose and albumin excretion. Hence AML is preferable to initiate antihypertensive therapy in type 2 diabetic Nigerians.

Key words: Antihypertensive therapy, Efficacy, Metabolic effects, Amlodipine and hydrochlorothiazide, Hypertensive type 2 diabetic Nigerians

INTRODUCTION

Hypertension in blacks nay in diabetics, remains a serious vexing public health and clinical problem. Indeed, worldwide hypertension in patients with type 2 DM is a prevalent condition associated with substantial morbidity and mortality. [1] Concomitant hypertension triples the already high risk of coronary artery disease (CAD), doubles total mortality and stroke risk, and may be responsible for up to 75% of all cardiovascular disease (CVD) events as well as renal complications in patients with DM. [1-4] In sub-Saharan Africa, hypertension remains the most rapidly rising CVD affecting over 20 million people. [5-6] In Nigeria, according to the Non-Communicable Diseases Survey [7] and data from other studies [8-12] hypertension is the most common non-communicable disease with a prevalence rate of 25% while DM is the most common metabolic disease with a prevalence rate of about 8%. At the time of diagnosis, more than 50% of the type 2 diabetics are also hypertensive, a worrisome condition associated with widespread disability, excess mortality, reduced capacity for work and family/social life disruption among the indigenous people. [13-15]

Reducing BP in people with hypertension and diabetes decreases both macrovascular (CAD, cerebrovascular disease, peripheral vascular disease) and microvascular complications (retinopathy and photocoagulation, nephropathy, neuropathy, micro angiopathy). Clinical trials [16-20] using a variety of antihypertensive agents have demonstrated

that modest reductions of 9-11 mmHg in SBP decrease CVD events by 34-69% and microvascular complications (retinopathy and nephropathy) by 26-46% within just 2-5 years. Hitherto, most international guidelines [4,20-21] have recommended a target BP of <130/80 mmHg for hypertensive patients with DM but most recently, this threshold was raised to <140/90mmHg based, to a large extent, on data from randomized controlled clinical trials. [19-20, 22-23]

One of the limitations of the current literature is a lack of strong evidence comparing the effects of BP treatment according to demographic factors such as ethnicity and age. These factors are important because ethnicity may be a strong predictor of adverse events in patients with DM, [24-25] and age may change relative or absolute benefits of hypertension treatment, in part because of competing risks for death. [26] Also the effectiveness of different antihypertensive agents in BP lowering may vary by ethnicity and age. For example, in Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), [27] African-American participants did not respond to angiotensin converting enzyme inhibitors (ACEIs) as well as other participants and had a higher risk for stroke as a result. However, it is not clear how these results relate to the populations of Africans born and living in Africa with type 2 DM.

Choice of initial antihypertensive agents in patients with DM is difficult to define precisely given the conflicting

available evidence [22,25-29] which suggests that there are no obvious superior agents. However, for black patients without renal disease, the weight of current evidence [22,25-31] recommends that thiazides (eg HCZ) or CCBs (eg AML) are reasonable first choice agents. Even, regardless of race or diabetic status, the current US 8th Joint National Committee [22] recommends thiazides or CCBs instead of ACEIs or ARBs as first-line agents in patients over the age of 75 years who have impaired renal function due to the risk of hyperkalemia, increased creatinine and further renal damage from the latter agents. Although Punzi and Novrit [32] reported that ACEI/ARB control in low renin individuals is dose-dependent, it is however well documented that in hypertensive blacks of African descent, ACEIs and ARBs are not effective for initiating therapy unless combined with diuretics or CCBs. [30,32-36]

It is known that, compared with other ethnic groups, blacks are disproportionately affected by hypertension, with higher rates of disease related morbidity and mortality. Also, the coexistence of hypertension and diabetes in this group [13-15,37-38] dramatically and synergistically increases the risk of microvascular and macrovascular complications resulting in excess morbidity and premature mortality. [13-15,37-38] Unfortunately, there is still no consensus on the best first-line antihypertensive agent to initiate treatment in this people. Hence, for the foregoing reasons and based on our earlier observations [39-41] this randomized, open-label, prospective, two-centre study was undertaken to evaluate whether AML was superior to HCZ for initiating antihypertensive treatment in blacks with type 2 DM born and living in Nigeria. Therefore, this report supplements data which have appeared in studies cited above.

MATERIALS AND METHODS

Patients

Forty type 2 diabetic Nigerians (20M and 20F) with newly diagnosed essential hypertension (stages 1 and 2) aged 43-68 years and attending Central Hospital and Osigbemhe Hospital both in Auchi in Edo State of Nigeria were enlisted into this study between March 2008 and March 2009. The sample size was estimated based on the number of Nigerians [12] that are believed to have hypertension with concomitant type 2 DM, and to detect a difference of 1 unit in mean change in the measured variables, between both treatment arms with a power equal to 90% using a one sample t-test at a one-sided significance level of 0.05, requires 20 patients per group.

Enrolled participants had qualifying hypertension of BP >150/90 and ≤180/120 mmHg measured on at least 2 occasions in lying/supine, sitting and standing positions using standardized methods. [42] Excluded were patients with identifiable cause of the hypertension except type 2 DM, clinical evidence of cerebrovascular, cardiac, renal, hepatic, gastrointestinal or endocrinologic disease except type 2 DM, hypersensitivity to AML and HCZ or related drugs, history of smoking, alcohol intake, substance abuse or mental illness. Also disqualified were patients needing any concomitant medication (apart from oral antidiabetic drugs) eg digitalis, non-steroidal anti-inflammatory drugs, psychotropic drugs, monoamine oxidase inhibitors or oral contraceptives, that may interact with the trial drugs and pregnant or lactating females. Controls comprised the parallel age and sex-matched hypertensives on HCZ.

Ethics

The research protocol was reviewed and approved by the Ethics Committees of Irrua Specialist Teaching Hospital Irrua, Nigeria (Ambrose Alli University College of Medicine Teaching Hospital) and Central

Hospital Auchu, Nigeria. After suitable explanation of the study protocol in lay language, all literate patients gave informed written consent and the illiterates thumb-printed the consent form before the beginning of the study that was conducted in line with the Helsinki Declaration of 1975, as revised in 2000. [43]

Design of Study

Patients were examined by a standardized pre-tested questionnaire seeking information on demographic data, the history of hypertension, DM, current drugs if any, educational and social status, dietary habits, smoking and alcohol intake, etc. The 40 patients were randomized to AML and HCZ groups each comprising 20 patients (10 M + 10 F) using computer program-generated random numbers. Diabetes was treated and controlled well in 32 patients with oral hypoglycaemic agents viz a sulfonylurea (glibenclamide 5 mg once daily) and a biguanide (metformin 500 mg once or twice daily) and in 8 patients with gliclazide 80 mg once or twice daily.

Measurements: heights (m), weights (wt) (kg), BP (mmHg), pulse (bpm), heart rate (bpm), urine volume (ml/24h), urine glucose and albumin concentration (mg/dl)

A stadiometer scale (Seca model, UK) was used for measuring height, with no shoes on; and a beam balance (Hackman, UK) was used to measure wt while on light clothing. BMI was computed as wt divided by height squared. SBP and DBP were measured with a standard mercury sphygmomanometer (Riester Diplomat Presameter, Germany) using standardized methods [42] at the sitting, standing and supine positions; always between 8am and 10am. Radial pulse was taken at both hands at the beginning and then at the right hand at every visit. Heart rate was evaluated using the stethoscope diaphragm at the apex beat at every visit.

The volume of 24h urine collected was measured with a measuring cylinder and recorded. The need to carefully collect all urine passed between Sunday 7am and Monday 7am on evaluation days was well emphasized. Rapid quantitative detection of glucose and albumin in urine was done using dipstick Medi-Test Combi 2^R test strips (Macherey-Nayel GmbH, Dueren, Germany; Expiry date 2011).

Pharmacotherapy intervention

Patients in AML group were treated initially with AML 5 mg and the dose was doubled after 6 weeks if BP was not controlled while in HCZ group patients were treated with HCZ 25 mg, both medications being administered once daily. The outpatient treatment lasted 48 weeks. The patients were monitored closely and outcome measures evaluated at baseline before treatment and at the end of weeks 1, 3, 6, 12, 24, 36 and 48. Unequivocal patient identification was possible via a patient identification list consisting of the patient number, first name and surname.

The study medications AML and HCZ are licensed for long-term treatment of hypertension so that dangerous side effects due to the medicaments were not to be expected. AML 5mg and 10mg tablets (Amlovar^R), were donated by Neimeth International Pharmaceuticals Ikeja, Nigeria: NAFDAC Reg No A4-0333; Manufacturing Date 07-2007 and Expiry Date 07-2010. HCZ 25mg tablets (Esidrex^R) were donated by Novartis Pharma SAS Nigerian Representative, NAFDAC Reg No OL-3705, Manufacturing Date 08-2007 and Expiry Date 08-2010.

Course of study and methods for recording efficacy and safety

All patients were advised to maintain their usual diet (weight-maintaining no-salt-added diet) and regular physical activity but to avoid undue stress throughout the duration of the study. They were instructed

to take their drugs every morning. Each patient was observed for about 2 hours after taking medication drug for the first time. Adherence in respect of intake of medication was encouraged by interviewing patients through phone calls, sporadic visits, pill counts outside the view of patients as well as urine volume measurements. To preclude white-coat effect, observer bias and to accurately assess the efficacy of the drugs, patients were followed up repeatedly at weeks 1, 3,6,12, 24, 36, and 48. At each visit, volunteered or spontaneous report of adverse events were assessed for severity and association with treatment; and the attending physicians/investigators also recorded any adverse events they observed themselves or elicited from the patient through careful interrogation like “How do you feel?” No patient withdrew from the study because of adverse events.

Response to therapy was defined as a decrease in the mean trough sitting SBP and DBP of 10 mmHg or a drop to < 90 mmHg with reduction of > 5 mmHg. BP was regarded as controlled if the DBP was < 80 mmHg and SBP < 130 mmHg. The effects of treatment on the various variables (except height) were assessed by comparing the

values at each visit with the pretreatment baseline values.

Statistical analysis of data

Data are presented as mean ± SEM or mean ± SD (for age, height and weight) using the Proc ANOVA of SAS (2004). Where significant differences were noticed, mean separation was carried out using Duncan Multiple Range Test. Correlation between two sets of variables was determined using Spearman’s rank correlation. $P < 0.05$ was regarded as significant.

The detail methodology and study procedure are given in our previous reports on this study population. [39-41]

RESULTS

As shown in Table 1, 20 patients were randomized to the AML and HCZ groups and each group was divided into 2 subgroups of 10M and 10F. At baseline, no significant difference was detected in the means of ages, BMIs, and SBPs/DBPs. However, subjects were relatively younger with high BMIs and significant (stage 2) hypertension. No patient was lost to follow - up throughout the study, perhaps because of the free treatment they were enjoying.

Table 1: Demographic characteristics and baseline blood pressures of hypertensive diabetic subjects (N = 20 [10M + 10F] per group)

Group	Characteristics	Male		Female	
		Range	Mean±SD/SEM*	Range	Mean±SD/SEM*
AML	Age (yrs)	46-61	53.90±5.04	45-62	53.10±5.38
	Height (m)	1.59-1.73	1.66±0.04	1.58-1.71	1.64±0.05
	Weight (kg)	74-90	83.20±5.13	72-89	80.0±4.71
	BMI. (kg/m ²)	29.37-30.10	30.25±0.24	28.92-30.48	29.00±0.70
	SBP(mm Hg)	150-180	164.50±3.76*	155-180	166.50±2.24*
	DBP(mm Hg)	100-115	104.50±1.89*	100-110	105.00±1.57*
HCZ	Age (yrs)	45-65	52.40±6.75	43-68	54.50±7.73
	Height (m)	1.62-1.74	1.68±0.04	1.58-1.70	1.64±0.03
	Weight (kg)	77-90	84.51±4.32	63-86	76.44±6.54
	BMI (kg/m ²)	29.39-30.00	29.96±0.19	26.30-29.76	27.50±0.53
	SBP(mm Hg)	98-180	162.50±3.71*	150-180	162.00±2.62*
DBP(mm Hg)	90-115	104.50±1.89*	100-115	102.50±2.71*	

Characteristics and blood pressures are not significantly different between the groups and hypertensives are relatively younger with high BMIs; AML, Amlodipine; HCZ, Hydrochlorothiazide; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; M, male; F, female;

*, Standard error of mean

The effects of treatment drugs on SBPs and DBPs in the trial subjects are presented in Table 2. The duration of treatment effect on the variables was significant ($P < 0.0001$) because at week 6, while on AML 5mg, 2 patients (2M) had their DBP < 90 mmHg and at week 12 while all the patients were on AML 10mg, 5 patients (4M + 1F) had DBP < 90 mmHg. At week 48, 11 patients (4M + 7F) had their DBP < 90 mmHg whereas 6 patients (3M +

3F) had BP $< 130/80$ mmHg. For HCZ group, no patient had DBP < 90 mmHg at week 6; at week 12, 4 patients (1M + 3F) had DBP < 90 mmHg and at week 48, 4 patients (2M + 2F) had their SBP/DBP $< 130/80$ mmHg. Overall, the mean M vs F SBP/DBP decrease from baseline was 27.0/17.5 vs 29.5/20.0 mmHg for AML group and 23.5/17.5 vs 22.0/16.5 mmHg for HCZ group.

Table 2: Effects of initiating therapy with AML and HCZ for 48 weeks on BP (mmHg) in type 2 hypertensive diabetic subjects.

Week	BP	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
		AML	HCZ	AML	HCZ	
0	SBP	164.50±3.76	165.00±3.71	166.50±2.24	162.00±3.59	
	DBP	103.60±1.89	104.50±1.89	104.50±1.57	102.50±2.71	
1	SBP	161.50±3.17	162.00±3.51	163.00±2.49	160.00±3.33	
	DBP	100.50±1.17	102.00±2.49	102.00±1.33	100.00±2.69	
3	SBP	158.50±3.58 _A	157.50±3.75 _A	161.50±1.98 _A	156.50±2.48 _A	
	DBP	99.00±0.69 _A	97.50±2.01 _A	98.00±1.33 _A	98.00±2.49 _A	
6	SBP	151.50±2.99 _B	152.50±2.81 _B	156.00±2.21 _B	151.00±3.15 _B	
	DBP	90.00±2.11 _B	94.00±1.63 _A	93.00±1.50 _B	92.00±1.53 _B	
12	SBP	146.50±2.36 _C	148.50±2.99 _C	152.00±1.70 _B	146.50±2.79 _C	0.320 ^{NS}
	DBP	87.50±1.54 _C	87.50±1.17 _B	90.50±1.17 _B	88.00±1.53 _C	0.877 ^{NS}
24	SBP	142.50±2.14 _C	146.50±3.34 _C	145.00±2.17 _C	145.00±3.07 _C	
	DBP	86.50±1.50 _B	87.00±1.34 _B	89.50±0.50 _C	87.50±1.71 _C	
36	SBP	142.00±2.00 _C	143.00±3.59 _D	141.00±1.94 _D	142.00±3.82 _D	
	DBP	86.00±1.63 _C	87.00±1.53 _B	88.00±1.33 _C	86.00±1.80 _C	
48	SBP	137.50±2.61 _D	141.50±3.42 _D	137.00±2.26 _D	140.00±3.58 _D	
	DBP	86.00±1.63 _C	87.00±1.53 _B	84.50±1.57 _D	86.00±1.80 _C	

Significant differences within columns are indicated by ABCD ($P < 0.05$): There are significant time-dependent reductions in BP in groups; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; AML, amlodipine; HCZ, hydrochlorothiazide; NS, not significant; (N = 10 per subgroup)

Table 3: Effects of initiating therapy with AML and HCZ for 48 weeks on heart rate (bpm) in type 2 hypertensive diabetic subjects

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	74.00±1.37	73.40±0.99	72.20±1.05	74.40±1.11	0.278 ^{NS}
1	74.20±1.44	72.80±1.05	72.20±1.05	74.20±1.29	
3	75.00±1.27	73.80±1.05	73.20±0.95	74.40±1.11	
6	76.20±1.47	73.40±1.07	74.20±0.87	74.40±1.11	
12	76.40±1.39	73.40±1.08	74.20±0.87	74.40±1.11	
24	76.40±1.45	73.20±1.12	74.00±0.89	74.80±1.08	
36	75.80±1.28	73.20±1.12	74.00±0.89	74.80±1.08	
48	75.80±1.28	73.20±1.12	74.00±0.89	74.80±1.08	

Heart rate is neither significantly affected by treatment nor by time; other abbreviations are as used in Table 2

Treatment, time or gender effect did not significantly affect the heart rate (HR) (Table 3). The effects of treatment drugs on 24h urine volume are presented in Table 4. Treatment and gender effects were not significantly different in the groups.

However, the time-dependent effect was significant ($P < 0.001$) because AML caused a maximum mean M vs F % diuresis of 3.6 v 5.1 at week 12 and HCZ 8.2 vs 6.9, respectively at week 3. Diuresis decreased soon after towards baseline particularly in

HCZ group. Urine volume was positively correlated with age ($r= 0.2003, P=0.0003$).

Table 4: Effects of initiating therapy with AML and HCZ for 48 weeks on 24h urine volume (ml) in hypertensive diabetic subjects

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	1483.00±27.21	1472.00±33.56	1460.00±22.31	1489.00±26.10	0.898 ^{NS}
1	1501.00±27.67	1565.00±36.06	1485.00±21.92 ^b	1567.00±30.55 ^a	
3	1521.00±27.10	1593.00±27.21 _A	1516.00±22.76	1591.00±30.60 _A	
6	1536.00±26.41	1520.00±28.40	1530.00±22.80	1536.00±27.01	
12	1538.00±26.05	1498.00±32.28	1534.00±21.09 _A	1517.00±25.12	
24	1525.00±25.70	1492.00±32.52	1516.00±22.57	1506.00±25.48	
36	1506.00±27.86	1487.00±33.67	1488.00±22.99	1504.00±25.43	
48	1504.00±28.10	1483.00±33.13	1466.00±22.12	1498.00±27.28	

Significant differences within columns are indicated by AB and within rows by ab ($P < 0.05$): There is significant time-dependent diuresis that peaked at weeks 12 and 3 in AML and HCZ subgroups, respectively; other abbreviations are as used in Table 2.

Table 5: Effects of initiating therapy with AML and HCZ for 48 weeks on urine glucose (mg/dl) in hypertensive diabetic subjects

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	37.00±5.18	38.00±5.18	35.00±5.00 ^b	47.00±4.99 ^a	0.361 ^{NS}
1	37.00±5.18	36.00±3.06	35.00±5.00	40.00±3.33	
3	40.00±3.33	40.00±3.33	40.00±3.33	38.00±3.27	
6	31.00±4.33 ^a	38.00±3.27 ^b	34.00±2.68 ^b	47.00±6.68 ^a	
12	32.00±2.00 ^a	40.00±3.33 ^b	36.00±3.06	42.00±3.27	
24	36.00±3.06	38.00±3.27	34.00±2.67	38.00±3.27	
36	36.00±3.06	38.00±3.27	34.00±2.6	38.00±3.27	
48	34.00±2.67	38.00±3.27	34.00±2.67	38.00±3.27	

Significant differences within rows are indicated by ab ($P < 0.05$): Treatment effect is significant and mean values tend to decrease in AML subgroups; other abbreviations are as used in Table 2

Table 6: Effects of initiating therapy with AML and HCZ for 48 weeks on urine albumin (mg/dl) in hypertensive diabetic subjects

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	15.00±1.00	22.00±1.97	15.00±2.55	15.00±1.00	0.312 ^{NS}
1	15.00±1.00	22.0±1.97	15.00±1.00	15.00±1.00	
3	15.00±1.00	22.00±1.97	21.00±0.92 _A	15.00±1.00	
6	17.00±1.19	22.00±1.97	21.00±0.92 _A	15.00±1.00	
12	15.00±1.00	25.00±1.91	21.00±0.92 _A	15.00±1.00	
24	17.00±1.97	9.00±0.92 _A	2.00±0.92 _B	6.00±0.80 _A	
36	9.00±0.92 _A	6.00±0.80 _A	6.00±0.80 _B	3.00±0.60 _A	
48	6.00±0.80 _A	6.00±0.80 _A	3.00±0.60 _B	3.00±0.60 _A	

Significant differences within columns are indicated by AB and within rows by ab ($P < 0.05$): There is a significant time-dependent decrease in mean values in all subgroups; abbreviations are as used in Table 2

Neither the time-dependent nor gender effect affected the urine glucose concentration significantly (Table 5). However, the treatment effects on the variable was significant ($P < 0.005$) and by week 48, mean M vs F % decrease was 8.1/2.9 in AML group and increase 2.7/2.1 in HCZ group, respectively. Although

treatment and gender effect did not significantly affect the urine albumin concentration in the 2 groups but the time-dependent effect was significant ($P < 0.0003$) as shown in Table 6, such that at week 48, mean M vs F decrease in baseline urine albumin was as follows: 9.0 vs 12.0 and 16.0 vs 12.0 mg/dl in AML and HCZ

groups, respectively. Urine albumin was positively correlated with SBP ($r= 0.2478$, $P= 0.0001$) and DBP ($r= 0.1363$, $P= 0.0147$).

DISCUSSION

The patients who participated in this study were recruited from 6 Local Government Areas in Edo North Senatorial Zone (a rural/suburban district characterized by insecurity, unemployment and other deprivations) of Edo State in the Niger-Delta region of Nigeria. These conditions may have contributed to their severe (stage 2) hypertension. All the same, these patients may be representative of many Nigerian communities burdened by high prevalence and incidence of hypertension. [12,38]

In the present study, the mean ages of the patients reveal that they are relatively young, a phenomenon most probably due to a high premature mortality. [13-15,37-38] The patients also had high mean BMIs that may be explained by lack of exercise or by their high energy, low-protein, cassava, yam or maize-based diets. The high BMI values of these patients suggest that many of them may be victims of the metabolic syndrome. [44-45]

Attainment of BP goals in patients with DM is critical both to reduce the risk of cardiovascular events and to delay progression of renal diseases. Here lies the importance of an effective drug to initiate treatment. AML significantly reduced BP more than HCZ in this study, confirming previous reports. [28,46-47] Indeed, compared with other classes of antihypertensive agents, there is a greater frequency of achieving BP control with CCBs (such as AML) as monotherapy in elderly subjects and blacks, population groups in which the low renin status is more prevalent. [48] Although optimal glycemic control has been shown to be an effective intervention in reducing microvascular and macrovascular

end-points in DM, [17] it has been suggested that aggressive BP control should be prioritized and stressed as the most important intervention in preventing adverse outcomes in the average population of persons with type 2 DM because of the dramatic beneficial effects of hypertension treatment which appear to be more effective than glycaemic control in reducing microvascular events, risk for CV events and mortality, and does so within a 4 to 6-year period. [4,25]

Although the control BP threshold for hypertensive patients with DM was $<130/80$ mmHg when this work was done, the new target BP of $<140/90$ mmHg does not in any way vitiate the present results. All the same, it is clear from the present study that it is unrealistic to think of attainment of low therapeutic BP targets of $< 130/80$ mmHg or $<140/90$ mmHg with antihypertensive monotherapy in nephropathy, retinopathy and stroke-prone blacks; [30] because the control rate was only 6 patients (30%) and 4 patients (20%) for AML and HCZ groups, respectively. In fact, for effective BP control in most cases, combination therapy or “therapeutic cocktails” are the rule. [31,49-55] Combination therapy with AML generally leads to better BP control and increase patient compliance. Hence, apart from combination treatment with diuretics, [49-50] AML has been used in combination with ACEIs [51] and ARBs. [52]

In this study, HCZ and not AML caused a robust diuresis that peaked at week 1 and decreased sharply by week 3, justifying the use of low doses of this diuretic as increasing doses may not lead to increased diuresis but increased side effects. [29, 40, 53-54] The positive correlation between 24h urine volume and SBP/DBP in the 2 groups, explains the increased diuresis and the effectiveness of these drugs in treating low renin volume-dependent hypertension in blacks. [34, 53-54]

We observed that, initiation of antihypertensive treatment with AML appeared to have a more favorable effect on urine glucose excretion than HCZ. Generally, it is commonly reported that poor blood sugar control in DM is less common with AML than with HCZ. [31,55-56] However, posthoc analysis of ALLHAT after an 8-year follow-up showed that fasting blood glucose levels increased in older patients regardless of antihypertensive agent used, with chlorthalidone showing the highest increase, AML the next highest and lisinopril the least. [57]

As first-line therapy, Punzi and Punzi [58] reported increased new onset diabetes with diuretic versus ACEI/CCB. According to a more recent report by Messerli et al, [59] in the analysis of 6 trials enrolling 30 842 hypertensives, diuretics resulted in a strong trend (22%) towards increased risk of new-onset DM compared with placebo, suggesting that the risk is due to the medication itself. Also, when compared with other antihypertensive agents, diuretics conferred a 35% increased risk of new-onset DM. Accumulating evidence [60-63] has confirmed that CVD and mortality increase in hypertensive diuretic users who developed hyperglycemia even when BP was well controlled. Indeed, CVD incidence had a direct dose response relation with diuretic use, with frequent users having the highest rate. [64] However, in contrast to the aforementioned studies, Kostiset al [65] in a follow-up of the Systolic Hypertension in the Elderly Persons (SHEP), found no significant increase in CV events in patients who had DM associated with chlorthalidone therapy.

In this study, within all patient groups, AML caused a more significant reduction in urine albumin than HCZ. Despite some conflicting reports, most studies showed lowering effects of CCBs such as AML on urine albumin excretion in

hypertensive non-diabetic and diabetic patients with micro-albuminuria or incipient nephropathy while their efficacy in overt nephropathy remains uncertain. [66]

CONCLUSION

In conclusion, our study of hypertensive Nigerians with type 2 DM indicates that there are greater reductions in BP with AML in comparison to HCZ. Evidence has also been provided for a more beneficial effect of AML over HCZ on urine glucose and albumin excretion, thus suggesting that AML may be preferred to HCZ for initiating antihypertensive therapy in these patients. However, since the number of patients studied was small and the fact that glycosylated haemoglobin (HbA_{1c}) levels (which should have given more specific blood sugar levels) were not done due to certain constraints, caution should be exercised in extrapolating these results to hypertensive diabetic black patients in general.

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