

Efficacy of Initiating Therapy with Amlodipine and Hydrochlorothiazide or Their Combination in Hypertensive Nigerians

Godfrey B. S. Iyalomhe,¹ Eric K. I. Omogbai,² Ambrose O. Isah,³ Osigbemhe O. B. Iyalomhe,⁴ Folorunso L. Dada,⁵ Sarah I. Iyalomhe⁶

¹Department of Pharmacology and Therapeutics, College of Medicine, Ambrose Alli University, Ekpoma, Nigeria, ²Faculty of Pharmacy, Department of Pharmacology and Toxicology, University of Benin, Benin City, Nigeria, ³Department of Internal Medicine, College of Medical Sciences, University of Benin, Benin City, Nigeria, ⁴Department of Physiology, School of Medicine, Johns Hopkins University, Baltimore, MD 21205, USA, ⁵Department of Medical Laboratory Sciences, Irrua Specialist Teaching Hospital (ISTH), Irrua, Nigeria, ⁶Department of Public Health and Primary Health Care, Central Hospital, Auchi, Nigeria

Abstract

In order to evaluate whether amlodipine or hydrochlorothiazide would be preferable to initiate therapy, 90 untreated hypertensive Nigerians of both genders aged 31–86 years with blood pressure $>160/90$ and $\leq 180/120$ mm Hg were recruited into a randomized 48-week study. Patients, 30 each in amlodipine, hydrochlorothiazide, and amlodipine–hydrochlorothiazide groups, were treated, respectively, with amlodipine 5 mg for 6 weeks and the dose increased to 10 mg till week 12, after which hydrochlorothiazide 25 mg was added; hydrochlorothiazide 25 mg till week 6, after which amlodipine 5–10 mg was added; and amlodipine 5–10 mg + hydrochlorothiazide 25 mg. Body mass index, blood pressure, heart rate, and 24-hour urine volume were evaluated at baseline and at the end of weeks 1, 3, 6, 12, 24, 36, and 48. The primary efficacy variables were decreased in mean trough sitting diastolic and systolic blood pressure such that blood pressure $< 140/90$ mm Hg was regarded as normalized. At week 48 in the amlodipine group, 27 patients versus 25 patients in the hydrochlorothiazide group had diastolic blood pressure < 90 mm Hg (90% vs. 83.3%; $P < .03$). In the amlodipine group, 23 patients versus 20 patients in the hydrochlorothiazide group had blood pressure $< 140/90$ mm Hg (76.7% vs. 66.7%; $P < .01$). In the amlodipine–hydrochlorothiazide group, 27 patients (90%) and 15 patients (50%) had diastolic blood pressure < 90 mm Hg and blood pressure $< 140/90$ mm Hg, respectively. This study has demonstrated that a regimen of amlodipine to which hydrochlorothiazide is subsequently added provides superior efficacy on blood pressure control when compared with a regimen of hydrochlorothiazide to which amlodipine is subsequently added or with *ab initio* amlodipine–hydrochlorothiazide combination therapy.

Keywords: antihypertensive efficacy, initiating therapy, amlodipine, hydrochlorothiazide, hypertensive Nigerians

INTRODUCTION

Cardiovascular diseases (CVDs) have become a major cause of morbidity and mortality worldwide, and hypertension is a leading contributor to this phenomenon (1–3). In particular, Sub-Saharan Africa faces an unprecedented epidemic of CVDs with hypertension, which affects between 30% and 60% of African blacks, being the main driver of cardiovascular complications (4–6). In Nigeria, hypertension has a prevalence rate of 25% and is the commonest noncommunicable disease (5–7). It also remains the commonest cardiovascular cause of hospitalization and mortality (7–10). Indeed, in Nigeria, hypertension is on a worrisome public health trajectory.

It has been reported that black persons born and living in sub-Saharan African descent differ from white persons

and other populations with respect to cultural, social, and psychological roots, as well as in biological characteristics (5,11,12). Black persons are more likely to develop hypertension and, compared to other ethnicities, the disease is more severe in them with even greater tendency to have pressure-related organ injury such as left ventricular hypertrophy (LVH) (4,5). It is also more resistant to treatment and more likely to be fatal at an earlier age (6). According to the most recent data from the United States, the mortality rate due to hypertension is 2.72 times higher in blacks than in whites and the rate of stroke, coronary heart disease (CHD), and heart failure (HF) is higher in blacks compared with other ethnicities (13,14). Thus, hypertension seems to be a more aggressive disease in black patients, a phenomenon

Address correspondence to Godfrey B. S. Iyalomhe, Department of Pharmacology and Therapeutics, College of Medicine, Ambrose Alli University Ekpoma, Nigeria. E-mail: goddyiyalo@yahoo.com

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that has important implications for the choice of antihypertensive agents (3,12,15,16).

Until now there is no consensus on the optimum drug treatment strategy for hypertension in black patients (1,12,17,18). Some guideline panels (1,19–22) advise the use of a specific drug, usually a diuretic, as first-line treatment for uncomplicated essential hypertension (unless there are compelling indications for the use of another agent, e.g., in a patient with gout). However, one panel (Hypertension in African-Americans Working Group) of the International Society on Hypertension in Blacks (ISHIB) (23,24) has continued to advocate the use of a renin–angiotensin–aldosterone system (RAAS) inhibitor, whereas emerging evidence (17,18,25) favors the use of a calcium channel blocker (CCB).

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (the largest study of antihypertensive monotherapy ever performed) was intended to identify the best first-line treatment for high-risk hypertensive patients. However, despite its size and the numerous resulting publications, its implications and authority have continued to be disputed (26,27). Thus, the search for an ideal first-line drug or combination drugs for the treatment of hypertension in blacks remains controversial and continues to elicit attention, debate, and study. Though the question of whether it is preferable to initiate antihypertensive therapy with CCBs in blacks instead of the recommended low-dose thiazides continues to surface, it has not yet been widely investigated. Therefore, to our knowledge, this study, which is the first of its kind in Nigeria, was designed to evaluate whether amlodipine (AML), hydrochlorothiazide (HCZ), or their combination was preferable to initiate antihypertensive therapy in Nigerians in the light of current recommendations.

METHODS

Study Subjects

Enrolled into the study were 90 Nigerians (45 males (M) and 45 females (F)) with newly diagnosed essential hypertension (stages 1 and 2) aged 31–86 years, who were attending Central Hospital and Osigbembe Hospital, both in Auchi, Edo State, Nigeria, between March 2008 and March 2009. The sample size was estimated based on the number of Nigerians that are believed to be hypertensive (8). To detect a difference of two units 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, this requires 30 patients per group.

Eligible participants had qualifying hypertension of BP >160/90 and ≤180/120 mm Hg measured on at least two occasions in lying/supine, sitting, and standing positions using standardized methods (28). Excluded were patients with identifiable cause of the hypertension, clinical evidence of cerebrovascular, cardiac, renal, hepatic,

gastrointestinal, and endocrinologic disease, hypersensitivity to AML and HCZ or related drugs, history of smoking, alcohol intake, substance abuse, or mental illness. Also excluded were patients whose conditions or drugs may interact with the trial drugs: pregnant and lactating females and patients on digitalis, nonsteroidal anti-inflammatory drugs, psychotropic drugs, monoamine oxidase inhibitors, and oral contraceptives.

The research protocol was reviewed and approved by the Ethics Committees of Irrua Specialist Teaching Hospital (Ambrose Alli University College of Medicine Teaching Hospital), Irrua, Nigeria, and Central Hospital, Auchi, Nigeria. Before beginning the study, the protocol was explained in lay language. While all literate patients gave informed written consent, the illiterate patients thumb-printed the consent form.

Study Design

The subjects were examined by a standardized pretested questionnaire seeking information on demographic data, history of hypertension, current drugs, if any, educational and social status, dietary habits, smoking, and alcohol intake. The 90 patients were randomized to three groups (AML, HCZ, and AML-HCZ), each comprising 30 patients divided into subgroups of 15 M + 15 F using computer program-generated random numbers.

Measurement of Height, Weight, Heart Rate, and Blood Pressure

A stadiometer scale (Seca model, UK) was used for measuring height (m), with no shoes on, and a beam balance (Hackman, UK) was used to measure weight (kg) while in light clothing. Body mass index (BMI) was computed as weight divided by height squared. Heart rate (HR) was taken using the stethoscope diaphragm at the apex beat at every visit. Systolic BP (SBP) and diastolic BP (DBP) (mm Hg) were measured (on both arms on the first day) between 8 am and 10 am with a standard mercury sphygmomanometer (Riester Diplomat Presameter, Germany) using standardized methods (28) at the sitting, standing, and supine positions. Any constricting clothing on the upper arm was removed before any measurement, and the subjects were discouraged from talking or moving during the measurements. The first phase of the Korotkov sound was regarded as the SBP while the fifth phase was regarded as the DBP. Measurements were taken two consecutive times with an interval of at least 1 minute and the average recorded. During the study, the results of the BP measurement were not given to the subjects.

Antihypertensive Intervention

The patients in the AML group were treated initially with AML 5 mg, and the dose was doubled after 6 weeks (weeks) if BP was not controlled. Then after 12 weeks (end of monotherapy), HCZ 25 mg was added if the desired BP was not achieved. In the HCZ group, the

patients were treated initially with HCZ 25 mg for 6 weeks (end of monotherapy), after which AML 5 mg was added if the BP was uncontrolled. The dose of AML was doubled after 12 weeks if the BP was still not normalized. In the AML-HCZ group, the treatment was initiated with AML 5 mg + HCZ 25 mg. If the BP was not controlled after 6 weeks, the dose of AML was doubled. The outpatient treatment lasted 48 weeks. The patients were monitored closely with measurements taken before treatment and at the end of weeks 1, 3, 6, 12, 24, 36, and 48 of treatment. 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 dangerous side effects due to the medicaments were not to be expected. AML 5 and 10-mg tablets (Amlovar[®], reg no. A4-0333; manufacturing date 07-2007 and expiry date 07-2010) were donated by Neimeth International Pharmaceuticals, Ikeja, Nigeria. HCZ 25-mg tablets (Esidrex[®], reg no. OL-3705; manufacturing date 08-2007 and expiry date 08-2010) were donated by Novartis Pharma SAS Nigerian Representative (Benin City, Edo State).

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 for the first time. Adherence in respect of intake of medication was encouraged by interviewing patients through phone calls, sporadic visits, and pill counts outside the view of the patients. To preclude white-coat effect and observer bias, as well as to accurately assess the efficacy of the drugs, the 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 was 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 with regard to the BP measurement was defined as a decrease in the mean trough sitting SBP and DBP of 10 mm Hg or a drop to <90 mm Hg with reduction of >5 mm Hg. The BP was regarded as controlled if the DBP was <90 mm Hg and SBP < 140 mm Hg. The effects of treatment on the various variables (except height) were assessed by comparing the values at each visit with the pretreatment baseline values.

Collection of Urine Samples

Urine: Each subject collected a 24-hour urine sample into a plastic container from Sunday 7 am to Monday 7 am at

baseline (week 0) before treatment and on the evaluation days. The need to carefully collect all urine passed was well emphasized. The volume of the 24-hour urine was measured with a measuring cylinder and recorded on each evaluation day.

Data Analysis

All data are presented as mean \pm SEM or mean \pm SD (for age, height, and weight) using the general linear model procedure (PROC GLM) of the statistical analysis system (2004). Where significant differences were noticed, mean separation was carried out using the Duncan Multiple Range Test. The correlation between two sets of variables was determined using Spearman's rank correlation. $P < .05$ was regarded as significant.

RESULTS

As shown in Table 1, at baseline (week 0), there was no statistically significant difference observed in the M versus F patients in the AML, HCZ, and AML-HCZ groups, respectively, with regard to the means of ages, BMIs, as well as the SBP/DBP. Most of the patients had significant (stage 2) hypertension. The analysis excluded the data for a M patient in the AML group who travelled and so could not report for evaluation at week 48; a F from the AML group who became pregnant and so was withdrawn from the study between weeks 36 and 48 as well as a M patient whose week 36 result was lost in the AML-HCZ group.

The effects of treatment on the SBP and DBP in the trial subjects are shown in Table 2. At week 6 (during monotherapy) while on AML 5 mg, 11 patients (6 M + 5 F), i.e., 36.7% of subjects, had their DBP <90 mm Hg. By the end of monotherapy at week 12 while all patients were on AML 10 mg, 22 patients (12 M + 10 F), i.e., 73.3% of patients, had DBP < 90 while 3 patients (1M + 2F) had their BP normalized to <140/90 mm Hg. At the end of week 48, a total of 27 patients (14 M + 13 F), i.e., 90% of subjects, besides the 2 patients unavailable for assessment, had their DBP < 90 mm Hg while 23 patients (11 M + 12 F) had BP <140/90 mm Hg.

At the end of monotherapy (week 6) in the HCZ group, eight patients (4 M + 4 F), i.e., 26.7% of subjects, had their DBP < 90 mm Hg and no patient had normalized BP. At the end of week 12 while all patients were also on AML 5 mg, 15 patients (7 M + 8 F), i.e., 50% of subjects, had DBP < 90 mm Hg while 3 patients (1 M + 2 F) had their BP normalized. At the end of week 48 while 27 patients were also on AML 10 mg, a total of 25 patients (14 M + 11 F), i.e., 83.3% of subjects, had DBP < 90 mm Hg while 20 patients (12 M + 8 F), i.e., 66.7% of subjects, had their BP normalized.

At the end of week 6 in the AML-HCZ group, 16 patients (9 M + 7 F), i.e., 53.3% of subjects while on AML 5 mg + HCZ 25 mg, had DBP < 90 mm Hg and 1 M patient had BP normalized. At the end of week 12

Table 1. Demographic characteristics and baseline blood pressure of subjects in the AML, HCZ, and AML-HCZ treatment groups

Group	Characteristics	Male		Female	
		Range	Mean \pm SD/SEM ^a	Range	Mean \pm SD/SEM
AML	Age (y)	31–80	60.80 \pm 14.03	37–80	63.60 \pm 8.02
	Height (m)	1.59–1.74	1.66 \pm 0.04	1.56–1.76	1.66 \pm 0.07
	Weight (kg)	62–88	76.77 \pm 8.94	62–90.4	79.80 \pm 8.85
	BMI (kg/m ²)	24.84–29.75	26.50 \pm 0.80	25.48–30.13	27.50 \pm 0.31
	SBP (mm Hg)	150–175	162.50 \pm 2.82 ^a	150–180	165.67 \pm 3.00 ^a
	DBP (mm Hg)	100–115	103.00 \pm 1.75 ^a	90–115	105.33 \pm 2.04 ^a
HCZ	Age (y)	45–86	63.80 \pm 12.02	48–80	65.47 \pm 10.15
	Height (m)	1.61–1.80	1.69 \pm 0.05	1.12–1.76	1.67 \pm 0.04
	Weight (kg)	68–89	75.37 \pm 6.27	60–80	73.44 \pm 6.30
	BMI (kg/m ²)	26.25–27.47	26.50 \pm 0.32	23.17–26.67	24.50 \pm 0.42
	SBP (mm Hg)	160–180	170.33 \pm 2.09 ^a	160–180	169.00 \pm 1.90 ^a
	DBP (mm Hg)	95–115	104.67 \pm 1.50 ^a	90–115	104.67 \pm 1.98 ^a
AML-HCZ	Age (y)	42–78	62.13 \pm 11.89	48–87	69.93 \pm 11.60
	Height (m)	1.58–1.72	1.64 \pm 0.04	1.59–1.82	1.67 \pm 0.06
	Weight (kg)	65–87.5	74.33 \pm 7.07	65–90.2	77.21 \pm 8.67
	BMI (kg/m ²)	26.10–29.66	27.50 \pm 0.38	25.79–27.33	26.00 \pm 0.56
	SBP (mm Hg)	150–180	165.00 \pm 4.57 ^a	155–180	167.50 \pm 4.44 ^a
	DBP (mm Hg)	100–115	106.00 \pm 1.48 ^a	90–120	107.33 \pm 2.01 ^a

Notes: Abbreviations: Demographic characteristics and blood pressure are comparable in the groups; AML – amlodipine; HCZ – hydrochlorothiazide; AML-HCZ – amlodipine-hydrochlorothiazide combination; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure.

^aStandard error of mean ($N = 30$ [15 M + 15 F] per group).

while 29 patients (14 M + 15 F) were on AML 10 mg + HCZ 25 mg, 23 patients (12 M + 11 F), i.e., 76.7% of subjects, had DBP < 90 mm Hg and 7 patients (4 M + 3 F) had their BP normalized. However, at the end of week 48, a total of 27 patients (14 M + 13 F), i.e., 90% of subjects, had DBP < 90 mm Hg while only 15 patients (9 M + 6 F), i.e., 50% of subjects, had their BP normalized.

The time-dependent mean M versus F SBP/DBP decreases were significant ($P < .001$) such that at week 48 the values were 37.88/30.86 versus 37.75/31.76 (AML), 37.66/28.67 versus 34.33/27.34 (HCZ), and 33.00/30.33 versus 31.67/31.33 for the AML-HCZ subgroup. The gender effect was significant ($P < .0002$), for the differences in DBP in M values were higher than F.

From Table 3, it is observed that at week 12 AML caused a significant (10%–11% [$P < .0001$]) increase in HR equally in both M and F subjects. The HR, however, decreased toward baseline after this period. The gender effect was insignificant. The HR was negatively correlated with both SBP ($r = -0.2426$, $P < .0001$) and DBP ($r = -0.2370$, $P < .0001$).

The effects of study drugs on mean 24-hour urine volume in the subgroups are shown in Table 4. Only HCZ caused a significant ($P < .0001$) diuresis, which was maximal in both M and F subgroups at week 1. Diuresis decreased toward pretreatment values soon after. AML-HCZ caused the least maximum diuresis at week 3. The 24-hour urine volume was positively correlated with SBP ($r = 0.1963$, $P < .0001$), DBP ($r = 0.1173$, $P < .0017$), and HR ($r = 0.0825$, $P < .0272$).

DISCUSSION

The patients enrolled in this study were recruited from a rural/semi-urban district burdened by high unemployment rate, insecurity, shortage of housing, poverty, and many other deprivations. These conditions may have contributed to their severe (stage 2) hypertension (25). These patients may be representative of many Nigerian communities characterized by a high prevalence and incidence of hypertension (8–10,29). Although this study had an open-label design, seven repeated follow-ups were undertaken to preclude white-coat effect and observer bias, as well as to ensure high BP reproducibility and drug efficacy assessment.

At the end of monotherapy, the rate of BP control was higher for patients receiving AML than for those on HCZ because AML reduced BP more significantly than HCZ. Materson and coworkers (30,31), who studied the effects of single drug therapy in men including 291 blacks, reported that the CCB diltiazem, after 1 year, achieved the best control rate (56.8%), defined as a clinic DBP < 90 mm Hg, in blacks. Sareli et al. (25), who carried out a randomized open-label trial with 409 black hypertensives in Johannesburg, South Africa, reported that CCBs were more effective than thiazides as initial antihypertensive treatment in these patients. In a comprehensive systematic review of antihypertensive monotherapy in black patients, Brewster et al. (17) reported that only CCBs were the drug type effective for all BP outcomes in all subgroups of black patients, including those with a baseline DBP > 110 mm Hg.

Table 2. Effects of initiating therapy with AML, H CZ, and AML-H CZ combination on BP (mm Hg) in hypertensive subjects for 48 weeks

Week	BP	Treatment subgroups (male)			Treatment subgroups (female)			Gender Effect
		AML	H CZ	AML-H CZ	AML	H CZ	AML-H CZ	
0	SBP	169.67 ± 2.82	170.33 ± 2.00	168.00 ± 4.57	171.67 ± 3.00	169.00 ± 1.90	167.67 ± 4.44	
	DBP	103.00 ± 1.75	104.67 ± 1.50	106.00 ± 1.48	105.33 ± 2.03	104.67 ± 1.98	107.33 ± 2.00	
1	SBP	160.00 ± 0.00 ^A	162.67 ± 2.00 ^A	162.00 ± 3.78 ^A	160.00 ± 0.00 ^{bA}	157.34 ± 2.12 ^{bA}	165.67 ± 2.28 ^a	
	DBP	107.00 ± 1.16 ^a	102.33 ± 1.88	98.67 ± 1.92 ^{bA}	102.00 ± 1.16 ^a	99.67 ± 2.01 ^{bA}	100.00 ± 1.95 ^b	
3	SBP	157.00 ± 3.23 ^A	156.67 ± 2.32 ^B	155.00 ± 3.09 ^B	159.00 ± 3.17 ^A	152.33 ± 2.12 ^B	158.33 ± 2.66 ^A	
	DBP	90.67 ± 5.94 ^{bA}	95.67 ± 1.68 ^{aA}	91.67 ± 1.16 ^B	92.67 ± 1.82 ^A	95.33 ± 1.33 ^A	92.67 ± 2.48 ^B	
6 [§]	SBP	149.00 ± 2.85 ^B	150.33 ± 2.04 ^C	148.00 ± 3.27 ^C	155.33 ± 2.95 ^{aB}	147.33 ± 2.12 ^C	150.00 ± 2.39 ^B	
	DBP	87.00 ± 2.06 ^A	89.00 ± 1.48 ^B	84.33 ± 1.45 ^C	87.33 ± 1.28 ^B	90.67 ± 1.88 ^B	86.00 ± 2.14 ^C	
12 [§]	SBP	145.67 ± 2.38 ^B	144.33 ± 1.75 ^D	142.67 ± 2.62 ^D	149.33 ± 3.04 ^{aC}	142.00 ± 2.00 ^{bD}	143.33 ± 1.99 ^{bC}	0.198 ^{NS}
	DBP	79.33 ± 2.00 ^B	84.00 ± 1.63 ^C	80.00 ± 1.76 ^D	83.33 ± 1.93 ^C	85.33 ± 1.33 ^C	82.67 ± 1.82 ^D	
24	SBP	140.67 ± 1.75 ^C	138.00 ± 1.48 ^F	136.68 ± 2.05 ^E	140.67 ± 2.00 ^D	139.33 ± 1.53 ^D	139.00 ± 1.63 ^D	
	DBP	76.33 ± 1.42 ^B	80.00 ± 1.38 ^D	78.67 ± 1.98 ^D	80.00 ± 1.95 ^C	79.67 ± 1.42 ^D	80.33 ± 1.86 ^D	
36	SBP	134.67 ± 1.86 ^D	134.00 ± 1.22 ^F	136.00 ± 1.56 ^E	135.72 ± 1.63 ^E	136.00 ± 1.22 ^D	138.00 ± 1.53 ^D	
	DBP	75.00 ± 1.29 ^B	77.33 ± 1.53 ^D	76.67 ± 1.87 ^E	77.14 ± 1.94 ^D	78.67 ± 1.65 ^D	78.67 ± 1.92 ^D	

Notes: Significant differences ($P < .05$) within columns are indicated by ABCDEF, and within rows by ab. Significant treatment effect occurred in weeks 1–12 and all treatment regimens significantly decreased SBP and DBP.

Abbreviations: SBP – systolic blood pressure; DBP – diastolic blood pressure; AML – amlodipine 10 mg; H CZ – hydrochlorothiazide 25 mg; AML-H CZ – amlodipine 5–10 mg/hydrochlorothiazide 25 mg combination; SEM – standard error of mean; NS – not significant ($N = 15$ per subgroup).

[§]Combination treatment: weeks 24–48 (AML), weeks 12–48 (H CZ); *** $P < .001$.

Table 3. Effects of initiating therapy with AML, HCZ, and AML-HCZ combination on heart rate (bpm) in hypertensive subjects for 48 weeks

Week	Treatment subgroups (male)			Treatment subgroups (female)			Gender Effect
	AML	HCZ	AML-HCZ	AML	HCZ	AML-HCZ	
0	75.67 ± 1.45	74.93 ± 1.38	77.73 ± 0.70	74.67 ± 1.21	75.47 ± 1.21	76.80 ± 2.00	0.183 ^{NS}
1	77.20 ± 1.48	78.93 ± 1.30	78.93 ± 0.61	76.73 ± 1.20	76.93 ± 1.23	77.47 ± 1.18	
3	78.80 ± 1.50 ^B	77.47 ± 1.13	79.20 ± 0.78	78.13 ± 1.06 ^B	78.00 ± 1.32	78.80 ± 1.01	
6	82.40 ± 1.33 ^A	77.33 ± 1.10	79.87 ± 2.7	81.53 ± 1.05 ^A	77.73 ± 1.25 ^b	78.80 ± 1.17	
12 ^S	82.93 ± 1.51 ^{aA}	77.3 ± 1.08 ^b	79.73 ± 0.70	82.73 ± 0.99 ^{aA}	77.60 ± 1.11 ^b	78.80 ± 1.18 ^b	
24 ^S	82.27 ± 1.19 ^{aA}	77.3 ± 1.08 ^b	79.33 ± 0.67 ^b	82.00 ± 0.59 ^{aA}	77.47 ± 1.07 ^b	78.40 ± 1.16 ^b	
36	81.07 ± 1.07 ^{aA}	77.33 ± 1.15 ^b	79.20 ± 0.64	81.29 ± 0.50 ^{aA}	77.46 ± 0.99 ^b	77.73 ± 1.12 ^b	
48	80.57 ± 0.85 ^{aA}	77.20 ± 1.15 ^b	79.33 ± 0.64	81.29 ± 0.40 ^{aA}	77.47 ± 0.99 ^b	77.60 ± 1.16 ^b	

Notes: Significant differences ($P < .05$) within columns are indicated by AB and within rows by ab. A significant increase in heart rate occurred in AML male and female subgroups.

Abbreviation: bpm – beats per minute; other abbreviations are as used in Table 2.

Furthermore, the main morbidity and mortality outcomes did not differ significantly between treatment groups when the drugs were combined to reach treatment goals. Indeed, low rates of BP control have been previously documented in black patients with hypertension who were receiving treatment with HCZ (32,33). Wright et al. (26) reported no significant differences in the primary outcome (combined fatal CHD or nonfatal MI) between chlorthalidone, AML, and lisinopril in black patients, but chlorthalidone was reported to be more effective than the other two in reducing secondary outcomes such as CVD and HF. Even then, AML treatment led to a greater decrease in DBP and in the incidence of stroke, but was associated with a higher relative risk of new-onset HF compared to chlorthalidone. In patients with established HF without systolic dysfunction, however, AML does not increase morbidity or mortality (34,35).

Many arguments have been raised against the ALLHAT conclusion that diuretics should be preferred for first-line antihypertensive therapy (36,37). From a logical point of view, secondary outcomes are, as stated in an earlier ALLHAT report (38), “soft data” to be used to “confirm or supplement the primary end point”. Since the primary outcomes did not differ among the drugs, there is insufficient evidence that diuretics are superior to AML and lisinopril. Even then, AML has been adjudged to be a preferred treatment in the elderly subjects and blacks with normal renal function or microalbuminuria, population groups in which the low renin status is prevalent (17,39).

At week 12, the rate of BP control assessed by the primary efficacy variable, i.e., decrease in mean trough sitting DBP to <90 mm Hg, was 73.3%, 50%, and 76.7% for the AML, HCZ, and AML-HCZ groups, respectively. Thus in support of Tejada et al. (40) and the Blood Pressure Lowering Trialists’ Collaboration (41), it was relatively faster to have BP control through combination therapy. However, it was surprising that the control rate at week 48 was 90% versus 76.7% (AML), 83.3% versus 66.7% (HCZ), and 90% versus 50% (AML-HCZ combination) for DBP < 90 mm Hg versus BP $< 140/90$ mm Hg, respectively. Why the percentage

of subjects normalized to $<140/90$ mm Hg in the AML-HCZ group was the smallest is uncertain. Compensatory physiological mechanisms due to initial sudden decrease in BP may increase release of vasoconstrictors (e.g., angiotensin II, norepinephrine, vasopressin, and endothelin), which may in turn lead to increased SBP (36). Another implication of this finding is that since both AML and HCZ address the low renin volume-dependent hypertension in blacks, combination of either drugs with another having a different mechanism of action may yield better BP control (18).

Combination therapy with AML generally leads to better BP control and increases patient adherence (18,42–49). Hence, apart from combination treatment with diuretics (42), AML has been used in combination with angiotensin-converting enzyme inhibitors (ACEIs) (18,43) and angiotensin II receptor blockers (ARBs) (44,45). Furthermore, recent studies have also added AML in combination regimes that include more than two antihypertensive agents of different classes, and these triple (46,47) and quadruple (48) combinations have demonstrated increased efficacy and appropriate safety profiles. Most recently, Odili et al. (49), in the progress report on the first sub-Saharan trial of newer versus older antihypertensive drugs in native black patients born and living in Africa, reported that BP control can be achieved faster in black patients with once daily AML/Valsartan 5/160 mg combination instead of once daily bisoprolol/HCZ 5/6.25 mg combination.

It was only in the HCZ group that we observed a significant diuresis that peaked at week 1 and then 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 (1,50). The positive correlation between 24-hour urine volume and SBP/DBP explains the increased diuresis and the effectiveness of these drugs in treating low renin volume-dependent hypertension in blacks (4,37,50). A surprising and unexpected observation in this study was that AML-HCZ combination treatment caused the least diuresis and this may further explain why this group had the lowest percentage of patients normalized to BP $< 140/90$ mm Hg. Our findings confirm earlier

Table 4. Effects of initiating therapy with AML, HCZ, and AML-HCZ combination on 24-h urine volume (mL) in hypertensive subjects for 48 weeks

Week	Treatment subgroups (male)			Treatment subgroups (female)			Gender Effect
	AML	HCZ	AML-HCZ	AML	HCZ	AML-HCZ	
0	1437.33 ± 53.44	1393.33 ± 37.74	1458.00 ± 45.11	1438.67 ± 55.87	1390.00 ± 41.75	1478.67 ± 46.83	0.439 ^{NS}
1	1523.33 ± 57.34	1621.33 ± 36.49 ^A	1506.00 ± 42.26	1486.00 ± 56.09	1586.67 ± 37.01 ^A	1514.67 ± 45.30	
3	1560.67 ± 48.37	1488.67 ± 38.23	1520.00 ± 42.55	1514.00 ± 57.77	1476.00 ± 34.79	1528.67 ± 46.00	
6	1571.33 ± 48.37 ^a	1424.67 ± 38.16 ^b	1500.00 ± 45.66	1559.33 ± 58.95	1418.00 ± 36.82	1528.00 ± 47.99	
12 ^S	1578.67 ± 43.62 ^a	1436.00 ± 35.18 ^b	1504.67 ± 43.26	1535.33 ± 55.32	1432.67 ± 38.46	1516.67 ± 47.43	
24 ^S	1560.00 ± 40.05 ^a	1418.67 ± 35.66 ^b	1488.00 ± 43.21	1500.00 ± 50.86	1418.67 ± 40.01	1497.33 ± 46.33	
36	1524.00 ± 36.33 ^a	1400.00 ± 36.31 ^b	1461.33 ± 43.19	1472.86 ± 42.06	1390.67 ± 42.17	1478.67 ± 45.82	
48	1478.57 ± 32.71 ^a	1394.67 ± 36.38 ^b	1448.00 ± 42.66 ^a	1433.57 ± 36.08	1388.00 ± 39.59	1476.00 ± 45.16	

Notes: Significant differences ($P < .05$) within columns are indicated by AA and within rows by ab. Significant increase in diuresis is seen in HCZ male and female subgroups; other abbreviations are as used in Table 2.

reports of the clinically insignificant effects of study drugs on HR as well as on the M and F genders, indicating that dosage adjustments are not necessary in the sexes (25,31,50).

In conclusion, this study has demonstrated that in hypertensive Nigerians, initiating therapy with a regimen of AML to which HCZ is subsequently added provides superior efficacy on BP control when compared with a regimen of HCZ to which AML is subsequently added or with *ab initio* AML-HCZ combination therapy. This information, which contrasts with the current recommendations, will be helpful in addressing the problem of hypertension control, especially in Nigeria. However, because of the small number of patients studied, caution should be exercised in interpreting our results or extrapolating our findings to hypertensive black patients in general. Further research is necessary.

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