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## A comparative evaluation of fixed dose and separately administered combinations of lisinopril and hydrochlorothiazide in treatment-naïve adult hypertensive patients in a rural Nigerian community

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### ABSTRACT

**Background:** Antihypertensive drugs administered as fixed dose combination (FDC) therapy compared to separately administered combination therapy have been proposed to improve treatment compliance/adherence, and therefore the efficacy of blood pressure (BP) control treatment.

**Aim:** The aim of this present study is to compare the blood pressure control, renal end-organ protection and medication compliance/adherence in patients receiving FDC and those receiving separately administered combinations of Lisinopril and Hydrochlorothiazide in treatment-naïve hypertensive adult patients in a rural Nigerian community.

**Method:** ology: This randomized two-arm prospective longitudinal 8-week parallel-group study was carried-out for 6-month at the Ajegunle Community between April 2018 and October 2018. Efficacy variables included the changes from baseline in mean sitting systolic BP (MSSBP) and mean sitting diastolic BP (MSDBP). Medication safety, compliance/adherence and renal end-organ protection were assessed.

**Results:** The baseline characteristics of the two groups were similar. Prevalence of hypertension was found to be 32.9%. The mean blood pressure of all the participants was  $165.6 \pm 16.5$  mmHg and  $98.5 \pm 11.5$  mmHg for systolic BP and diastolic BP respectively, while the mean pulse rate of the participants was  $85.0 \pm 13.4$  beats/min. At the 8-week end point, both regimens had achieved significant reductions from baseline in MSSBP ( $-33.18$  and  $-37.16$  mm Hg, respectively; both,  $P < 0.05$ ) and MSDBP ( $-12.97$  and  $-17.53$  mm Hg; both,  $P < 0.05$ ). Both regimens were generally well tolerated. Adherence was better in the FDC arm and there was no any reported case of proteinuria occurrence in both arms.

**Conclusion:** The high prevalence of hypertension in the community shows that there is unmet need in diagnosis and awareness of the disease. Both combination therapies were well tolerated; but the FDC antihypertensive therapy resulted in statistically significant amount of BP reductions than the separately administered combination antihypertensive therapy. Making FDCs available and affordable will help many hypertensive patients to achieve their target BP control goals easily.

### 1. Introduction

Hypertension is highly prevalent in Nigeria and is a leading cause of stroke, heart failure, cardiovascular diseases and renal failure [1,2]. The prevalence of hypertension and antihypertensive prescription utilization patterns in Nigerian patients has been investigated and reported [3–6]. Some studies have also documented the prevalence of hypertension in

Nigeria to be 28.9% with urban (30.6%) being higher than rural (26.4%) patients [3,7].

Antihypertensives from different pharmacological classes are being used for therapy with agents that target the renin angiotensin system (RAS) playing a major central role as, the antihypertensive agents of choice [8]. Angiotensin converting enzyme inhibitors are effective antihypertensive drugs that act by inhibiting the conversion of

**Abbreviations:** FDC; Fixed Dose Combination; BP; Blood Pressure; MSSBP; Mean Sitting Systolic Blood Pressure; MSDBP; Mean Sitting Diastolic Blood Pressure.

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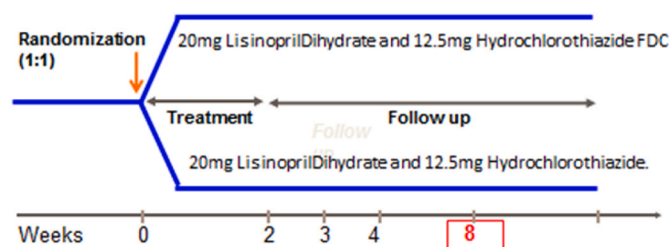


Fig. 1. Study design.

angiotensin I to physiologically active angiotensin II. Angiotensin II plays a central role in the pathogenesis of hypertension because it has a potent vasoconstriction effect and stimulates aldosterone secretion. Thus inhibiting this pathway may be expected to lead to effective anti-hypertensive outcome [9]. Despite proper drug therapy, many patients with hypertension are not at the targeted BP control goal with only about 30% of people with hypertension being adequately treated and have their blood pressure controlled over time [10,11].

The Joint National Commission (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends the use of two or more antihypertensive agents to achieve the desired BP goals [12,13]. The ACE inhibitor lisinopril is a widely used long acting anti-hypertensive drug that is recommended for use at once daily doses. Its combination with low dose hydrochlorothiazide has proven to be effective in most patients [14–16].

Adverse effects, drug availability and cost have been identified as reason for patients' poor adherence or compliance to treatment. Medication non-adherence is a major problem among patients with hypertension and is one of the main causes of failure to adequately control BP [17,18]. The development of single-pill combinations of two antihypertensive agents, commonly known as a fixed-dose combination (FDC) therapy, is the solution to overcoming non-adherence or non-compliance to treatment. A single pill containing more than one antihypertensive agent with different mechanisms of action (as opposed to multiple agents given separately) is likely to have a beneficial impact on medication adherence-taking behavior, as it simplifies the treatment regimen. Single pill combinations (SPCs) provide additional BP – lowering compared with component monotherapies and a great proportion of patients may reach BP goal by starting earlier on SPCs. Furthermore, SPCs may improve adherence/compliance and persistence with therapy [19,20]. Increase albumin excretion in urine (albuminuria) may underlie the presence of renal disease to cardiovascular diseases [21]. The National Kidney Foundation guidelines for the assessment of proteinuria recommend screening adults using the

albumin-to-creatinine ratio or an albumin-specific dipstick in single untimed urine sample [22].

The main purpose of this present study is to compare the effectiveness of fixed dose combination (FDC) therapy and separately administered combination therapy of lisinopril and hydrochlorothiazide in treatment-naïve hypertensive adult patients in a rural Nigerian community. In addition, we evaluated for medication tolerability (safety),

Table 2

Mean for age, blood pressure level and pulse rate according to gender.

Parameters	All participants (N = 129)	GROUP A (N = 64)		GROUP B (N = 65)	
		Lisinopril-Hydrochlorothiazide Fixed-dose combination (Number)		Lisinopril-Hydrochlorothiazide Separately administered (Number)	
		Males (N = 28)	Females (N = 36)	Males (N = 39)	Females (N = 26)
Age	47.225 ± 9.5	47.14 ± 10.6	48.47 ± 7.4	46.39 ± 9.9	46.85 ± 10.4
Systolic BP	165.57 ± 6.5	171.89 ± 16.2	167.47 ± 19.0	164.0 ± 14.1	158.50 ± 14.1
Diastolic BP	98.50 ± 11.5	97.1 ± 9.7	98.81 ± 11.5	100.08 ± 12.6	97.23 ± 12.1
Pulse rate	84.969 ± 13.4	85.5 ± 13.0	87.11 ± 11.8	85.10 ± 15.0	81.27 ± 13.2

Table 3

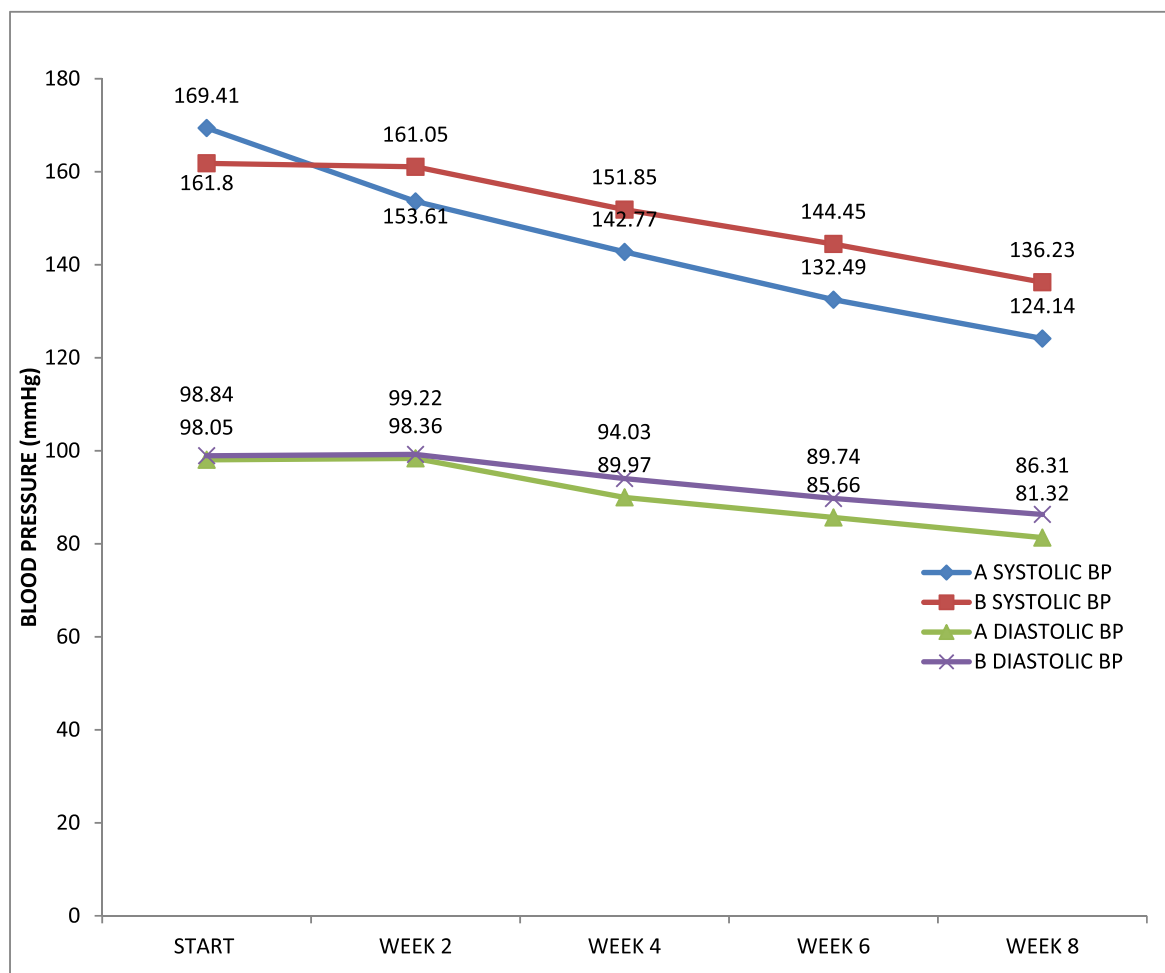
Blood Pressure levels for hypertension occurrence according to gender.

BP (mmHg)	GROUP A Lisinopril-Hydrochlorothiazide Fixed-dose combination (N)		GROUP B Lisinopril-Hydrochlorothiazide Separately administered (N)		Total (Number)
	Male	Female	Male	female	
<b>Systolic BP (mmHg)</b>					
140–159	8	10	15	11	44
160–179	10	19	18	11	58
180 & Above	10	7	6	3	26
Isolated Systolic hypertension	–	–		1	1
Total	28	36	39	26	129
<b>Diastolic BP (mmHg)</b>					
90–99	14	16	11	13	54
100–109	5	10	10	5	30
110 & Above	4	4	10	3	21
Isolated diastolic hypertension	5	6	8	5	24
Total	28	36	39	26	129

Table 1

Participants demographic characteristics and physiological parameters.

Parameters	Lisinopril-Hydrochlorothiazide Fixed-dose combination (N = 64)	Lisinopril-Hydrochlorothiazide Separately administered (N = 65)	Total (N = 129)
	Number (%)	Number (%)	Number (%)
Gender			
Male	28 (43.75)	39 (60)	67 (51.94)
Female	36 (56.25)	26 (40)	62 (48.06)
Age (years)			
<30	1 (1.56)	0	1 (0.77)
30–59	57 (89.06)	56 (86.15)	113 (87.60)
≥60 yr	6 (9.38)	9 (13.85)	15 (11.63)
Body mass index (kg/m <sup>2</sup> )	27.0 ± 7.1	27.0 ± 6.8	27.0 ± 4.2
Blood pressure (mmHg)			
Systolic	169.41 ± 17.9	161.80 ± 14.2	165.57 ± 16.5
Diastolic	98.05 ± 10.7	98.94 ± 12.4	98.50 ± 11.5
Pulse rate (beats/min)	86.39 ± 13.9	83.57 ± 14.3	84.97 ± 13.4
Urine protein	0	0	0
Previous antihypertensive treatment	0	0	0



**Fig. 2.** Effects of treatment on mean systolic and diastolic blood pressure over time. A: fixed-dose combination therapy group B: separately administered combination therapy group.

the presence of proteinuria and adherence/compliance to treatment regimen in the two-arm groups of participants. This present study extends the current body of knowledge by the fact that the chosen patient population is primarily African participants and it is an interesting development to observe a study with socio-culturally diverse mixed black African participants' background; as some of the previous similar studies [12,13,15,16,29,40,52–54] conducted in other regions of the world were carried-out amongst the white Caucasian patient population with some different genetic variability & phenotypic characteristics [12, 13,15,16,29,40,52–54].

## 2. Methodology

### 2.1. Study sites and setting

This randomized two-arm prospective longitudinal 8-week parallel-group study was carried-out for 6-month at the Ajegunle Community between April 2018 and October 2018. This community is situated along Ikorodu road in Kosofe Local Government Area of Lagos State, Nigeria. The community is made up of people from different parts of Nigeria. It has an estimated land area of 81 km<sup>2</sup> and a population of about 665,393 as of the 2006 national census [23]. The screening of the community members to identify hypertensive individuals and the subsequent inclusion of these hypertensive individuals in the present study took place at the Ajegunle Community Primary Health Centre.

### 2.2. Study population and inclusion criteria

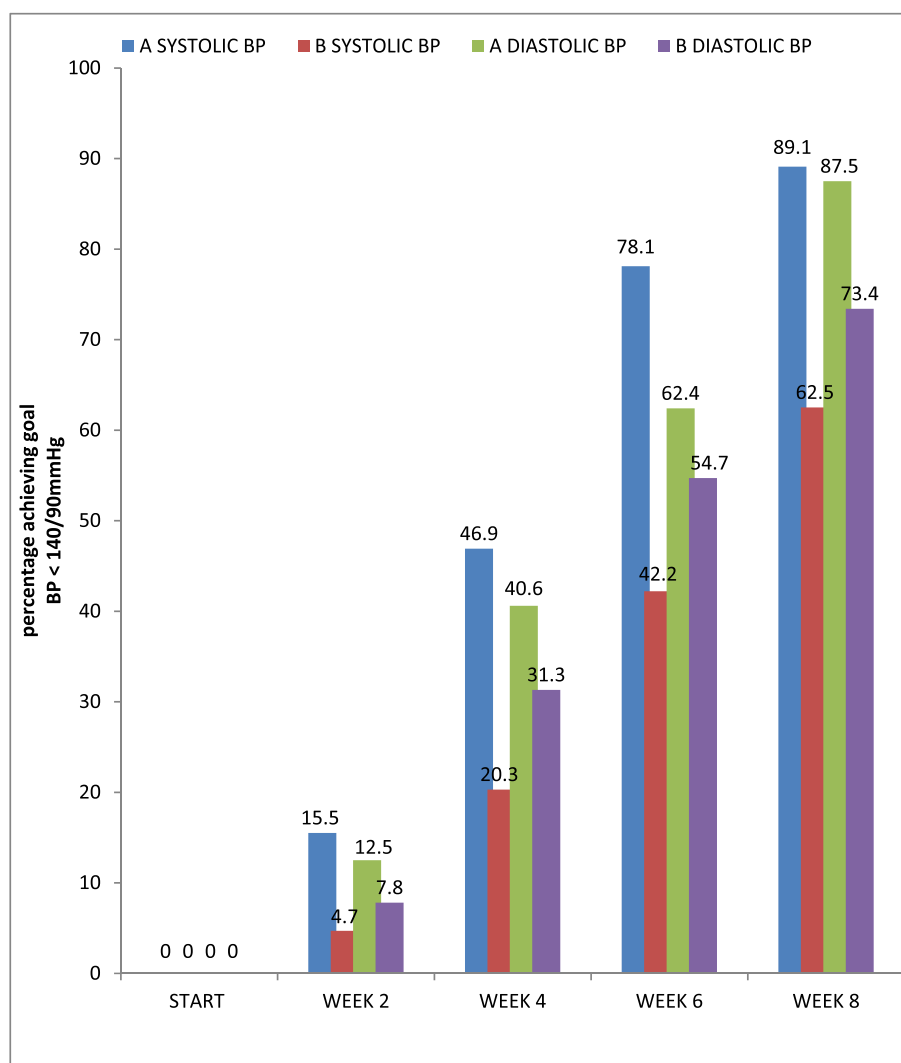
The present study recruited and enrolled treatment naïve male and female adult individuals, aged >18 years with confirmatory diagnosis of hypertension from the organized community screening done and were residing within the Ajegunle community as at the time of this present research. They were found to be hypertensive during the organized screening of the community members. In this present study, hypertension was defined as a resting state sitting position blood pressure (BP) of  $\geq 140/90$  mm Hg at baseline repeated on at least 3 different occasions of BP check and still found to be elevated above this stipulated cut-off point.

### 2.3. Exclusion criteria

The present study excluded hypertensive individuals who were already on antihypertensive drugs as at the time of this present study, pregnant women, breast-feeding women, individuals below 18 years of age, individuals with systolic BP > 210 mm Hg and/or diastolic BP > 120 mm Hg, individuals with complications of hypertension including stroke, heart failure, cardiac arrhythmia, hypertensive retinopathy and/or renal impairment as at the time of initial presentation during recruitment contact for this study.

### 2.4. Study design and sample size

This was a randomized two-arm prospective longitudinal 8-week



**Fig. 3.** Percentage of all participants attaining blood pressure goal of <140/90 mmHg over time. A = Fixed-dose combination; B = Separately administered combination.

parallel-group study carried-out for 6-month at the Ajegunle Community between April 2018 and October 2018. There was screening of adult members of the community. Blood pressures were categorized based on both the current American College of Cardiology/American Heart Association (ACC/AHA) 2017 guidelines and the preexisting Joint National Committee on Hypertension (JNC 7) categories [24,25]. These patients who had hypertension were randomized into any of the two groups and then asked to sign the informed consent forms. Those in group A received fixed dose combination (FDC) therapy of antihypertensive comprising 20 mg Lisinopril dihydrate and 12.5 mg Hydrochlorothiazide, while those in group B received separately administered combination therapy of 20 mg Lisinopril dihydrate and 12.5 mg Hydrochlorothiazide. The study design is shown in Fig. 1 below.

Using the single population sample size formula  $Z^2pq/d^2$  [26], with an estimated hypertension prevalence (p) of 13.2% obtained in a previous study [10], an assumption of 95% level of confidence ( $Z = 1.96$ ), and a 5% (0.05) margin of error (d) tolerated; an estimated sample size of about 176 participants having high blood pressure of 140/90 mmHg or above was calculated. But during the study, the research investigators were able to recruit only 142 participants who agreed to sign their informed consent form for enrollment. These consented participants were randomly allocated into two different treatment arm groups of A and B; out of which 129 participants completed the 8 weeks follow-up visit. But 12 participants absconded during the follow-up visit period with no any

known specific reason(s), while 1 participant was withdrawn from the study due to continuous and persistent elevation of her BP above the value of 210/120 mmHg not permitted or allowed for this present study despite antihypertensive combination therapy with both Lisinopril and Hydrochlorothiazide combination (that is; antihypertensive drug resistance to both 20 mg of Lisinopril dihydrate and 12.5 mg of Hydrochlorothiazide combination). Each study group treatment lasted for 8 weeks duration with follow-up monitoring done at every 2 weeks interval.

## 2.5. Study objectives and target endpoint

The primary objectives and target endpoint of this present study was to compare the percentage of hypertensive adult patients achieving a reduction in BP of  $\geq 15$  mm Hg (if baseline diastolic BP was <110 mm Hg) or  $\geq 20$  mm Hg (if baseline diastolic BP was  $\geq 110$  mm Hg); the percentage of patients achieving a BP goal of <140/90 mm Hg. Other secondary objectives include evaluating for the occurrence of proteinuria and medications adherence during 8 weeks of a daily treatment regimen with fixed dose combination (FDC) therapy of antihypertensive comprising of 20 mg Lisinopril dihydrate and 12.5 mg Hydrochlorothiazide compared to separately administered combination therapy with 20 mg Lisinopril dihydrate and 12.5 mg Hydrochlorothiazide. Each study group treatment period lasted for 8 weeks duration and follow-up

**Table 4**

Number of Participants that achieved MSSBP and MSDBP goals in 4 weeks and in 8 weeks.

	MALE		FEMALE	
	ACHIEVED	NOT ACHIEVED	ACHIEVED	NOT ACHIEVED
<b>GROUP A</b>				
<b>4 weeks</b>				
Systolic blood pressure	9(32.1%)	19(67.9%)	21(58.3%)	15(41.7%)
Diastolic blood pressure	13(46.4%)	15(53.6%)	13(36.1%)	23(63.9%)
<b>8 weeks</b>				
Systolic blood pressure	23(82.1%)	5(17.9%)	34(94.4%)	2(5.6%)
Diastolic blood pressure	23(82.1%)	5(17.9%)	33(91.7%)	3(8.3%)
<b>GROUP B</b>				
<b>4 weeks</b>				
Systolic blood pressure	6(15.4%)	33(84.6%)	7(26.9%)	19(73.1%)
Diastolic blood pressure	12(30.8%)	27(69.2%)	8(30.8%)	18(69.2%)
<b>8 weeks</b>				
Systolic blood pressure	22(56.4%)	17(43.6%)	18(69.2%)	8(30.8%)
Diastolic blood pressure	26(66.7%)	13(33.3%)	22(84.6%)	4(15.4%)

GROUP A: Lisinopril-Hydrochlorothiazide fixed-dose combination (N = 64).

GROUP B: Lisinopril-Hydrochlorothiazide separately administered combination (N = 65).

monitoring was done at every 2 weeks interval.

## 2.6. Efficacy and safety assessments

The blood pressure (BP) and heart rate (HR) were assessed at each follow-up monitoring visit. Body mass index was determined from weight and height measured at the screening visit. Blood pressure (BP) and heart rate (HR) were measured after 15 min in resting state, at least two times (which were 5 min apart) in the sitting position. The respective blood pressure (BP) of each study participant was measured using validated manual analogue of the mercury sphygmomanometer by Accosons, England with appropriately sized cuff and Littman stethoscope for listening to the referenced Korotkoff pulse sounds' phases for both systolic BP and diastolic BP at the cubital fossa region of the fore arm. While the heart rate (HR) was assumed to be equivalent to the pulse

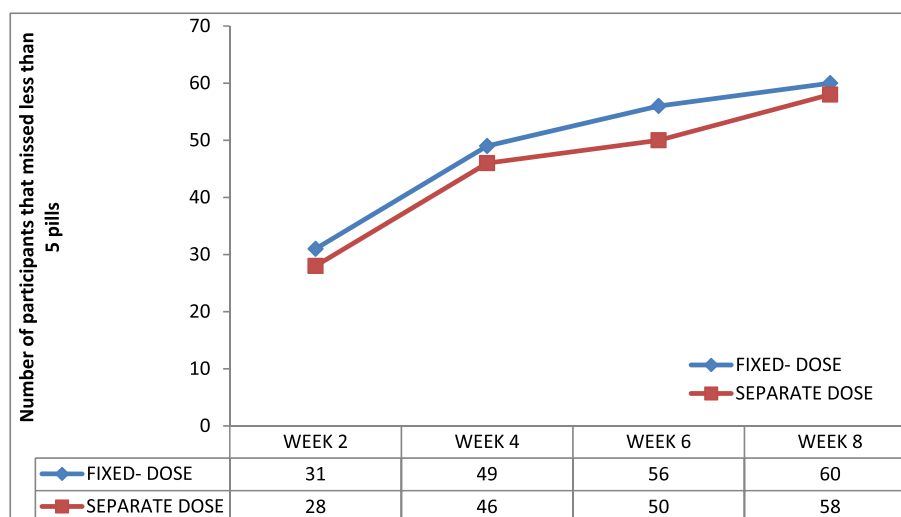
rate (PR) that was measured via palpation of the radial artery at the wrist region. All measurements were performed on the participants' non-dominant upper limb, which was the upper limb used for all subsequent readings throughout the study period. A repeat measurement was done at least 10 min later if the first measurement indicated high blood pressure within the hypertensive domain. Hypertension was defined in this present study as a resting state sitting position BP  $\geq 140/90$  mm Hg at baseline repeated on at least 3 different occasions of BP check and still found to be elevated above this stipulated cut-off point at the physician's office. The BP was considered not elevated if  $< 140/90$  mm Hg. All the antihypertensive medications used for this study was sourced by the investigators. The 20 mg of Lisinopril dihydrate and 12.5 mg of Hydrochlorothiazide combination used for the FDC therapy among the group A participants and for the separately administered combination therapy among the group B participants were administered as once daily therapeutic regimen.

## 2.7. Tolerability assessment and renal end-organ protection evaluation

Tolerability was assessed by collecting information about adverse drug events. A physical examination was performed at randomization (week 0) and at each visit until week 8. Any untoward event not present during the baseline recruitment visit or at the start of the study was recorded as an adverse drug event. The absence of proteinuria was used to evaluate for renal end-organ protection, but the presence of proteinuria indicated the occurrence of renal end-organ damage. Proteinuria was assessed at baseline and 8 weeks post randomization using three overnight urine samples. Adherence to drug treatment was monitored by pill counts for each of the patients in the two groups. The counts were performed at weeks 2, 4, 6 and 8. The medication-count adherence measure was computed as the total number of dosage units dispensed, minus the number of dosage units returned, divided by the number of dosage units dispensed, expressed as a percent [27,28].

## 2.8. Data analysis

The data were analyzed using the Statistical Package for Social Sciences [SPSS] version 23.0 software (SPSS Incorporation, Chicago, Illinois, USA) for descriptive and inferential statistics. The level of statistical significance was set at  $P < 0.05$ .



**Fig. 4.** Participants adhering to treatment regimen.

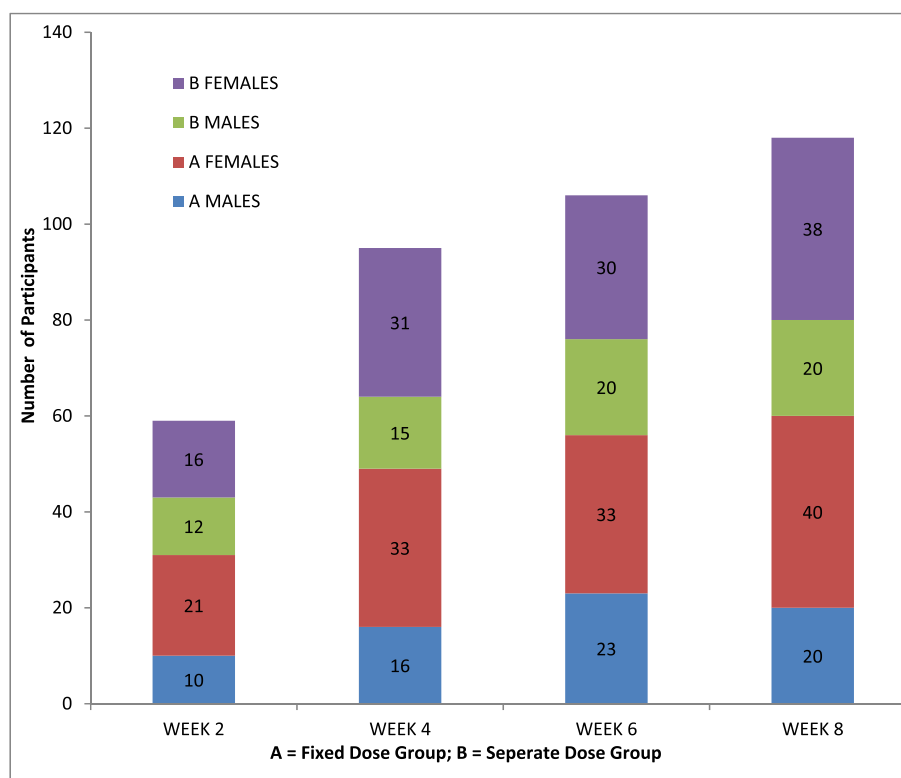


Fig. 5. Sex – associated adherence to treatment regimen.

### 3. Results

#### 3.1. Demographic characteristics of the study population

A total number of 577 adult persons were screened for high blood pressure in the Ajegunle Community, comprising of 257 (44.5%) males and 320 (55.5%) females. The total number of community members with hypertension was 190 persons out of which 94 (49.5%) were males, while 96 (50.5%) were females. But during this study, the research investigators were able to recruit only 142 participants who agreed to sign their informed consent form for enrollment. These consented participants were randomly allocated into two different treatment arm groups of A and B; out of which 129 participants completed the 8 weeks follow-up visit. But 12 participants absconded during the follow-up visit period with no any known specific reason(s), while 1 participant was withdrawn from the study due to continuous and persistent elevation of her BP above the value of 210/120 mmHg not permitted or allowed for this present study despite antihypertensive combination therapy with both Lisinopril and Hydrochlorothiazide combination (that is; antihypertensive drug resistance to both 20 mg of Lisinopril dihydrate and 12.5 mg of Hydrochlorothiazide combination). Each study group treatment lasted for 8 weeks duration with follow-up monitoring done at every 2 weeks interval.

Out of the 129 participants that completed the 8 weeks follow-up visit during this study; 67 (51.9%) were males, while 62 (48.1%) were females. The mean age of the study participants was  $47.2 \pm 9.5$  years. The baseline demographic and clinical characteristics of the 2 different treatment groups were similar. Table 1 shows the participants demographic characteristics and physiological parameters.

#### 3.2. Prevalence and pattern of hypertension

The total prevalence of hypertension in those screened in the community was 32.9% with a male-to-female distribution of 36.6% versus 30.0% respectively. There were very few cases of isolated systolic

hypertension and isolated diastolic hypertension. The mean blood pressure of all the participants were  $165.6 \pm 16.5$  mmHg and  $98.5 \pm 11.5$  mmHg for systolic BP and diastolic BP respectively, while the mean pulse rate of the participants was  $85.0 \pm 13.4$  beats/min. Only one person (female) had isolated systolic hypertension, while 24 persons (23 males and 11 females) had isolated diastolic hypertension. There was an increase in prevalence of hypertension with increasing age in both male and female participants, with more males than females having hypertension except for the age group of 50–59 years, where more females had increased systolic and diastolic hypertension in both group A and B participants. Mean for age, blood pressure level and pulse rate according to gender are presented in Table 2. While the blood pressure levels for hypertension occurrence according to gender are presented in Table 3.

#### 3.3. Efficacy

Mean sitting systolic BP (MSSBP) and mean sitting diastolic BP (MSDBP) were effectively reduced by the two treatments throughout the study ( $P < 0.05$ ). At the 8-week end point, both regimens had achieved significant reductions from baseline in mean MSSBP ( $-37.16$  mm Hg and  $-33.18$  mm Hg for group A and group B respectively;  $P < 0.05$ ), and mean MSDBP ( $-17.53$  mm Hg and  $-12.97$  mm Hg for group A and group B respectively;  $P < 0.05$ ). The changes in the mean sitting BP values in the two treatment groups at baseline, weeks 2, 4, 6, and 8 are shown in Fig. 2.

#### 3.4. Attaining goal BP and time to goal

The proportion of patients in each treatment group who attained the treatment goals of  $<140/90$  mm Hg was different. In both arms, more participants had their blood pressure (systolic and diastolic) controlled at the end of eight weeks. Again, more females than males in group A had their blood pressure (systolic and diastolic) controlled as compared to more males than females that had their blood pressure (systolic and diastolic) controlled in the group B participants. With regards to age,



there was no observed clear pattern of blood pressure control. However, within each age group, there was significant reduction in blood pressure of the participants after drug treatments in the two groups A and B. Fig. 3 shows the percentage of all participants attaining blood pressure goal of <140/90 mmHg over time, while Table 4 shows the number of participants that achieved MSSBP and MSDBP goals in 4 weeks and in 8 weeks.

### 3.5. Medication adherence & compliance

More patients adhered to treatment in the fixed dose combination group than the separately administered combination group. Pill counts showed that the number of patients that missed less than 5 pills was more in the fixed dose group. More females reported greater adherence to treatment than males in both groups. Fig. 4 shows the number of patients adhering to the two treatment regimens, while Fig. 5 shows gender-associated adherence to treatment regimen.

### 3.6. Tolerability and renal end-organ protection

Both combination therapies were well tolerated. There were no cases of adverse drug events among the participants in the two groups. Also, no report case of hypertensive complication was observed in each of the groups. There was no protein detected in the urine (by dipstick urinalysis) of the participants in the both group A and group B before and after the 8 weeks duration of this research study.

## 4. Discussion

Initial therapy for hypertension with a combination of drugs is recommended by both the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and European guidelines for patients whose blood pressures are 20/10 mm Hg or more above their targeted treatment goals [25,29]. JNC 7 guidelines recommend that thiazide diuretics be included in combination regimens. Combination antihypertensive therapy improves efficacy, tolerability, and patient adherence/compliance [19]. Fixed-dose combination therapy improves patient medication adherence/compliance through reduction of pill load, ease of use and the patients are more likely to remain on therapy if they attain adequate or optimal BP control with the initially prescribed combination of antihypertensive agents [20].

In this present study, we found that both lisinopril 20 mg-based treatments were effective in lowering BP. The antihypertensive efficacy is consistent with the direct action of angiotensin converting enzyme (ACE) inhibitors on the renin-angiotensin-aldosterone system and may involve mechanisms that lead to increase tissue perfusion and peripheral vasodilation [30,31].

From this study the estimated prevalence of hypertension in Ajeunle community was 32.9% using the JNC-7 definitions. The prevalence of hypertension in this study was similar to other studies in Nigeria, West Africa and follows a global trend of increase in hypertension prevalence that has been associated with life-style changes and population growth as risk factors [2,9–11]. Furthermore these risk factors may play a role in this rural study setting. The differences in prevalence of hypertension in rural areas versus urban area have been reported and showed higher urban prevalence compared to rural settings [3,32–34].

Age is an important determinant of hypertension occurrence [35,36] as blood pressure increases with age [35]. In this study, the peak age of patients with hypertension in the study population was 40–49 years and this was similar to other previous reports from south-western Nigeria [36,37]. In this present study, it was found that the prevalence of hypertension was higher in men than women. This finding is similar and consistent to the other previous reports that found the prevalence of hypertension to be higher in men compare to women [10,38].

Patients in the fixed-dose group showed a higher reduction in their

blood pressure (both systolic and diastolic) compared with patients in the separately administered combination group. This is consistent with previous reports which showed that fixed-dose combination of antihypertensive drugs are more efficacious than separately administered combination of antihypertensive drugs [39,40]. This finding could be attributed to the reduce number of total pill burden, ease of oral administration and improve treatment medications compliance/adherence associated with fixed dose combination (FDC) therapy than separately administered combination therapy [39,40].

Uncontrolled hypertension is associated with serious end-organ damage such as heart disease, stroke, renal impairment and blindness, but these complications can be prevented by adequate blood pressure control [41]. We did not detect proteinuria before and after treatment among the study participants in both groups. Macroalbuminuria predicts stroke and coronary heart disease, as well as overall mortality and end-stage renal disease [42,43]. High systemic blood pressure leads to increased intraglomerular pressure, which in turn brings about mesangial cell hypertrophy and extracellular matrix production, basement membrane thickening and growth-factor production [44]. Hence, reduction of blood pressure is essential to prevent progression of renal damage [45].

Drug non-adherence may prove to be the greatest barrier to the effectiveness of antihypertensive therapy and negatively impacts the prevention of cardiovascular and renal complications [46]. There are several methods to measure drug adherence, each of them having their own advantages and demerits [47]. Pill counting is a good measure of drug adherence commonly used in both clinical trials and clinical practice [48]. The apparent improvements in blood pressure levels associated with the use of fixed-dose combination therapy observed in this study may be a consequence of improved compliance with antihypertensive drug therapy. Higher adherence level was reported among patients receiving the fixed dose combination therapy regimen.

There was no report of any serious adverse drug events among members of the two-arm groups during the study. The short duration might not have allowed for adequate monitoring of adverse drug reaction occurrence. Other limitations of this study include the non-assessment of the level of salt intake and alcohol consumption by the participants. Only proteinuria evaluation was done. A spot albumin/creatinine ratio, serum creatinine level, creatinine clearance and estimated glomerular filtration rate (eGFR) may have detected renal dysfunction [49]. The pill count method is subject to various informational drawbacks including the reasons for not taking drugs, the timing, the reality of ingestion of pills removed from containers and could overestimate drug adherence [50]. To fully assess tolerability and safety; biochemical investigations would need to be conducted [51].

## 5. Conclusion

The high prevalence of hypertension in Ajeunle community reveals that there is an unmet need in the diagnosis and awareness of the hypertension among this populace. The drugs were effective in both groups with the fixed-dose combination antihypertensive therapy being more effective in getting more participants to the attainment of targeted blood pressure goal than the separately administered combination antihypertensive therapy. This is probably due to the enhanced adherence/compliance among those on fixed-dose combination therapy which offers simple dosage schedule/regimen and improves patient medication compliance and treatment outcomes. Therefore, pharmaceutical companies should make the fixed-dose combination antihypertensive therapy of lisinopril–hydrochlorothiazide regularly available and affordable in the pharmaceutical drug market; so as to help many hypertensive patients to achieve their target BP control goals easily through the enhancement of proper adequate antihypertensive medications adherence/compliance process.

## Executive summary

- In this study, the high prevalence of hypertension in Ajegunle Community reveals that there is unmet need in diagnosis and awareness of the disease.
- Both combination therapies were well tolerated; but the FDC antihypertensive therapy resulted in statistically significant amount of BP reductions than the separately administered combination antihypertensive therapy.
- Pharmaceutical companies should make the antihypertensive FDCs of lisinopril–hydrochlorothiazide regularly available and affordable in the pharmaceutical drug market; so as to help many hypertensive patients to achieve their target BP control goals easily through the enhancement of proper adequate antihypertensive medications adherence/compliance process.

## Ethics approval

This study was approved by the Health Research and Ethics Committee of the Lagos University Teaching Hospital (LUTH), Idi-Araba with the assigned Protocol Identification Number (PIN): ADM/DCST/HREC/APP/849.

## Study participants' welfare

This present study followed international, national, and/or institutional guidelines for the benevolent treatment of human study participants; and it also complied with the relevant standard legislations.

## Informed consent

Written informed consent was obtained from all the recruited participants before enrolment in this study. Furthermore, permission to conduct this study at Ajegunle Community was duly obtained from the Community Development Association (CDA) and the community leaders. Health education on risk factors for hypertension was also offered to the community members.

## Trial registration

Not applicable.

## Declaration of competing interest

None to declare; as there is no any conflict of interest among the authors.

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