Received: 15 September 2022 | Revised: 21 December 2022 | Accepted: 23 December 2022

DOI: 10.1111/jch.14632

ORIGINAL ARTICLE

WILEY

Fixed-dose combination therapy-based protocol compared with free pill combination protocol: Results of a cluster randomized trial

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Abstract

Fixed-dose combination (FDC) therapy is recommended for hypertension management in Nigeria based on randomized trials at the individual level. This cluster-randomized trial evaluates effectiveness and safety of a treatment protocol that used two-drug FDC therapy as the second and third steps for hypertension control compared with a protocol that used free pill combinations. From January 2021 to June

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Clinical Trial Registration: NCT04158154.

2021, 60 primary healthcare centers in the Federal Capital Territory of Nigeria were randomized to a protocol using FDC therapy as second and third steps compared with a protocol that used the same medications in free pill combination therapy for these steps. Eligible patients were adults (≥18 years) with hypertension. The primary outcome was the odds of a patient being controlled at their last visit between baseline to 6-month follow-up in the FDC group compared to the free pill group. 4427 patients (mean [SD] age: 49.0 [12.4] years, 70.5% female) were registered with mean (SD) baseline systolic/diastolic blood pressure 155 (20.6)/96 (13.1) mm Hg. Baseline characteristics of groups were similar. After 6-months, hypertension control rate improved in the two treatment protocols, but there were no differences between the groups after adjustment (FDC = 53.9% versus free pill combination = 47.9%, cluster-adjusted $p = .29$). Adverse events were similarly low (<1%) in both groups. Both protocols improved hypertension control rates at 6-months in comparison to baseline, though no differences were observed between groups. Further work is needed to determine if upfront FDC therapy is more effective and efficient to improve hypertension control rates.

KEYWORDS
cluster-randomized trial, fixed-dose combination, free pill combination, hypertension, Nigeria

1 | INTRODUCTION

Elevated blood pressure (BP) is the world's leading cause of mortality and cardiovascular disease, with a higher burden in low-and middle-income countries (LMICs).[1] Out of 1.4 billion adults (≥20 years) with elevated blood pressure globally, 36.9% received BP-lowering drugs, and only 13.8% had their BP controlled.[1–3] In Nigeria, the age-standardized hypertension prevalence is estimated to be 38% with suboptimal awareness (60%), treatment (34%), and control (12%) rates.[4]

Although most patients with hypertension require two or more drugs to achieve optimal control,[2,5,6] less than one-third of those treated receive such therapy.[2,7] Poor adherence to prescribed medications[2,8] and therapeutic inertia (i.e., lack of treatment intensification despite uncontrolled BP)[2,9] further contribute to poor BP control.[2] Prescription of upfront two-drug BP-lowering medications could increase the number of individuals with controlled BP by 80 million and could prevent ≥600,000 cardiovascular-related deaths over 5 years.[2] Treatment with fixed-dose combination (FDC) medicines is an emerging best practice for "safe, effective, rapid, and convenient" hypertension control, and thus, is included on the World Health Organization's Model List of Essential Medicines.[2,3,10] Combining two or more medicines in a single pill can be cost-effective and has important multi-level benefits, including: improved patient adherence to daily medication regimens; improved blood pressure control rates and shortened time to achieving blood pressure control; and more efficient hypertension management in healthcare facilities through simplification of drug supply and procurement logistics.[3,11,12]

In line with what previous evidence have shown, Nigeria's 2020 hypertension guidelines support the use of two-drug FDC if blood pressure is not controlled with single medicine therapy or when the initial treatment requires the use of two medications.[13] The guidelines recommend the use of appropriate medication combinations from different classes to maximize antihypertensive efficacy and minimize adverse effects of individual medication. Particularly, the guidelines recommend the combination of diuretic and calcium channel blocker (CCB) or another medicine selected from angiotensin converting enzyme inhibitor (ACEI), angiotensin-II receptor blocker (ARB), beta-blocker, alpha blocker or adding centrally acting agent to the diuretic or CCB for hypertension treatment due to the efficacy of this combination in Blacks.[13–16] The current study compared effectiveness and safety of a treatment protocol that used two-drug FDC based protocol for hypertension control compared with free pill combination based protocol for second or third steps treatment in primary healthcare centers (PHCs) in Nigeria using a cluster randomized trial design.

2 | METHODS

2.1 | Data source

Data were gathered from 60 PHCs in Abuja, Nigeria. The parent trial registration (NCT04158154) was updated to incorporate the current trial embedded within the HTN Program. The dataset generated and analyzed during the current study will be available in the National Heart, Lung, and Blood Institute's Biologic Specimen and Data

Repository Information Coordinating Center repository after completion of the HTN Program.

2.2 | Study design

This trial was embedded within the Hypertension Treatment in Nigeria (HTN) Program, a prospective, longitudinal type 2 hybrid study design to evaluate implementation and effectiveness of a multi-level, evidence-based implementation package in 60 public PHCs using an interrupted time series design.[17,18] The HTN Program was initiated in January 2020. PHCs with at least two full-time staff within the Federal Capital Territory, Nigeria, that were accessible to the study team by road and in all seasons, were functional (i.e., defined as open at least between the hours of 8 am to 4 pm and providing the minimum service package for primary healthcare centers), and were willing to participate were randomly selected through a multi-stage sampling frame.[18] To capitalize upon the availability of quality BP-lowering medicines and single pill combinations that are aligned with Nigeria's National Hypertension Treatment protocol, the study team embedded a pragmatic cluster-randomized trial to evaluate the effectiveness and safety of FDC therapy (Protocol 2) on hypertension control compared with the free pill combination (Protocol 1) over a 6-month follow-up period (Table S1). All 60 PHCs in the HTN Program were invited, and all agreed to participate as a cluster in this trial.

2.3 | Study population

Patients were eligible to participate in the HTN Program if they were 18 years and older and had hypertension (i.e., history of hypertension, or elevated SBP of ≥140 mm Hg, or elevated DBP of ≥90 mm Hg, or use of BP lowering medications if patients have BP lower than the thresholds and have documented history of hypertension). Individuals with missing or erroneous data on age, sex, or blood pressure or without meeting diagnostic criteria for hypertension were excluded. Women who were pregnant were registered and were then referred for specialist care in accordance with Nigeria's National Hypertension Treatment protocol. Further details about the study population have been reported.[17,18]

2.4 | Randomization and intervention

The study biostatistician (ASB) performed centralized, computer-generated randomization (1:1) at the cluster (i.e., PHC) level, stratified by baseline case load (above/below median), and baseline hypertension control rate (above/below median). Clusters were randomized to follow treatment steps based on Protocol 1 or Protocol 2 (Table S1). Patients were included in clusters through complete enumeration. PHCs were given medications according to the intervention allocation and were recommended to follow the Nigeria Hypertension Treatment Protocol for patient management and treatment, and the only difference between arms was whether medications for Steps 2 and 3 were provided as free pill combination (Protocol 1) or fixed-dose combination (Protocol 2) pills.

2.5 | Study procedures

At the patient level, data were collected within the PHCs by trained healthcare workers and record officers.[17] Particularly, patients' blood pressure measurements were taken in duplicate by a trained healthcare worker using an automated blood pressure monitor (Omron M3; HEM-7131-E, Kyoto, Japan) provided by the study team. We used the average of both blood pressure as the final blood pressure.[17] Blood pressures were measured after a 5-min rest period, and patients were seated with their back, arms, and feet supported. At the PHC level, data were collected by trained study team staff. The research team performed quarterly site monitoring and supportive supervision to ensure that blood pressures were measured accurately with additional on-site training provided as needed.

2.6 | Primary and secondary outcomes

The primary outcome was the adjusted odds of a patient being controlled, defined as blood pressure <140/<90 mm Hg at their last visit between baseline to 6-month follow-up in the FDC group compared to the single pill group. Secondary outcomes included: 1) between-group difference in the hypertension treatment rates, defined as the use of any BP-lowering therapy from baseline to 6 month follow-up, and measured at the individual patient level; 2) the adjusted odds of a patient being controlled, defined as blood pressure <130/<80 mm Hg at their last visit between baseline to 6-month follow-up, and measured at the individual patient level; 3) between-group difference in time to hypertension control, defined as the time from blood pressure ≥140/≥90 mm Hg to <140/<90 mm Hg over the study period, and measured at the individual patient level.

2.7 | Safety outcomes

Safety outcomes included between-group differences in the rates of 1) serious adverse events, 2) unanticipated problems, and 3) adverse events of special interest, including: cough, dizziness, swollen legs, and hypotension. To further capture safety data, five sites in each randomized group were selected based on staff strength and feasibility of on-site laboratory capabilities to collect serum electrolytes (i.e., sodium, potassium, chloride, and bicarbonate), urea, and creatinine at baseline and at 6-month follow-up.

2.8 | Statistical analysis

De-identified descriptive data were reported as means (standard deviation, SD) and medians (interquartile ranges, IQR) for continuous variables if data were skewed, and as proportions (95% CI) for

categorical variables. Baseline hypertension control rates were calculated by dividing the number of patients with systolic blood pressure (SBP) and diastolic blood pressure (DBP) <140/90 mm Hg by the total number of patients with hypertension. Data were analyzed overall, by treatment protocol and adjusted for cluster effect. In the first stage, all analyses were conducted based on available data from all patients who visited at least twice their PHC. In the second stage, an intention-to-treat analysis was undertaken based on data from all patients who visited all randomized PHCs during the period of the study.

For the primary outcome, we reported the adjusted odds of a patient being controlled, defined as blood pressure <140/<90 mm Hg at their last visit between baseline to 6-month follow-up in the FDC group compared to the free pill group. We also reported change in SBP and DBP from baseline to 6-month follow-up by treatment protocol group. In the primary analysis, we modeled the hypertension control as a binary outcome using a multilevel generalized linear mixed-effects modeling with a nested random effect for patients in each PHC and crossed random effect for visit time in months for each patient in each PHC. In the secondary analysis, the model was adjusted for age, sex, BMI, alcohol use, education, heart rate, and previous or new hypertension diagnosis. We tested the interaction effects between these covariates in the model.

Regarding the secondary outcomes, we reported the between-group difference in hypertension treatment rates from baseline to 6-month follow-up, the between-group difference in hypertension control rate, defined as blood pressure <130/<80 mm Hg from baseline to 6-month follow-up, and the between-group difference in the difference in time to hypertension control from baseline to 6-month follow-up. The Kaplan-Meier method to estimate the median time to hypertension control was used and a log-rank test to compare the time to hypertension control in both groups was performed. Safety outcomes were presented in proportions; no inferential statistics were performed for clinical adverse events because of the small number of events. Cluster-adjusted p-values were computed for laboratory adverse events using generalized linear mixed models.

In the intention-to-treat analysis, we assessed the mechanism of data missingness and eliminated the "Missing Completely at Random" hypothesis. We did this by firstly constructing all models without accounting for missing data, and secondly performing a sensitivity analysis, in which we performed several logistic regressions with binary variables (missing and not missing) and added other variables in the models as covariates. With the assumption that all missing data were missing at random (MAR), we performed multiple-imputation analysis using chained equations. We generated 20 amputated data sets with a maximum of 20 iterations. Variables included in the imputation model were systolic BP, diastolic BP, age, sex, weight, height, BMI, alcohol use, education, heart rate and previous or new hypertension diagnosis, and PHC including individuals.

In our context of unbalanced cluster size, we conducted a *post hoc* simulation-based power calculation using a generalized linear mixed model as an analytical method. We did a Monte Carlo power estimation based on 100 simulations using the following information: average number of patients per cluster (n = 74); clusters per arm (n = 30); proportion of hypertension control in protocol 1 at baseline (14.7%); proportion of hypertension control in protocol 2 at baseline (13.7%); proportion of hypertension control in protocol 1 at follow-up (47.9%); proportion of hypertension control in protocol 2 at follow-up (53.9%), and; a significance level of .05. We estimated that this study would have 75% power with a 95% CI [65.3%–83.1%].

A two-sided p-value <.05 was used to define statistical significance, and no adjustments were made for multiple comparisons. R version 4.2.1 (R Foundation, Vienna, Austria)[19] and SAS version 9.4 (SAS, Cary, NC, USA)[20] were used for statistical analyses.

3 | RESULTS

Figure S1 shows the flow of PHCs (n = 60) and patients. We recruited 4483 patients from 60 PHCs. Patients were ineligible and excluded if they were <18 years old, had SBP of <140 mm Hg or DBP of <90 mm Hg, and were not using BP-lowering medications (n = 56). The total number of patients was lower in Protocol 1 (n = 2046, 46.2%) compared with Protocol 2 (n = 2381, 53.8%) (95% CI = [−.10, −.05], cluster adjusted p-value <.01).

3.1 | Clusters and participants

Cluster level variables are reported in Table S2. PHCs randomized to Protocol 1 had fewer staff than PHCs in Protocol 2 (median [interquartile range] full-time staff: (15.4 [5, 65.5] versus 17.4 [11.5, 68], p < .01), but other cluster-level characteristics were similar.

Table 1 reports patients' baseline demographics and clinical characteristics, overall and by treatment protocol, which were generally similar. Patients' mean (SD) age was 49.0 (12.4) years, 70.5% were females, and 26.7% had never attended school. Mean (SD) body mass index was 28.0 (6.1) kg/m^2, and 4.6% of patients had a history of diabetes mellitus. Previously diagnosed hypertension was similar among patients randomized to Protocol 1 versus Protocol 2 (50.2% versus 53.8%, cluster adjusted p = .87). Other comorbid factors were uncommon, including chronic kidney disease (<.1%), stroke (<.1%), and heart attacks (<.1%).

Baseline mean SBP and DBP were similar between randomized groups (Protocol 1: 154 (20.4)/95(13.0) mm Hg versus Protocol 2: 155 (20.7)/96 (13.2) mm Hg). Baseline hypertension treatment and control rates were also similar between patients in Protocol 1 versus Protocol 2 (treatment = 97.3% versus 95.0%, cluster adjusted p = .25; control = 14.7% versus 13.7%, cluster adjusted p = .49).

3.2 | Primary analysis

Figure 1A shows the hypertension control rate at the last visit by treatment protocol among patients who had visited a PHC twice during the study period. Hypertension control rate was higher for patients randomized to FDC (Protocol 2) compared to free pill combination (Protocol 1, 53.9% vs. 47.9%, unadjusted p-value = .03), a difference

TABLE 1 Patient baseline demographics, and clinical characteristics overall and by treatment protocol group

Variable, no. (%)	Total (*N* = 4427)	Treatment received		Cluster adjusted *p*-value
		Protocol 1 (*n* = 2046)	Protocol 2 (*n* = 2381)	
Age, mean (SD), years	49 (12.4)	50 (12.0)	49 (12.7)	.85
Sex				.26
Male	1308 (29.5)	642 (31.4)	666 (28.0)	
Female	3119 (70.5)	1404 (68.6)	1715 (72.0)	
Body mass index, Mean (SD), kg/m^2	28 (6.1)	28 (6.1)	28 (6.1)	.22
Education				.54
Never attended	1179 (26.7)	614 (30.0)	565 (23.8)	
Primary	791 (17.9)	379 (18.5)	412 (17.3)	
Secondary	1186 (26.8)	468 (22.9)	718 (30.2)	
Higher	1219 (27.6)	574 (28.1)	645 (27.1)	
Other[a]	49 (1.1)	11 (.5)	38 (1.6)	
History of hypertension	2286 (51.9)	1094 (53.8)	1192 (50.2)	.87
History of diabetes	205 (4.6)	80 (3.9)	125 (5.3)	.73
History of chronic kidney disease	2 (<.1)	1 (<.1)	1 (<.1)	–
History of stroke	23 (.5)	8 (.4)	15 (.6)	.40
History of heart attack	6 (.1)	1 (<.1)	5 (.2)	–
Smoker/tobacco user	54 (1.2)	34 (1.7)	20 (.8)	.245
Alcohol user	188 (4.3)	105 (5.1)	83 (3.5)	.41
Systolic blood pressure, mean (SD), mmHg	155 (20.6)	154 (20.4)	155 (20.7)	.88
Diastolic blood pressure, mean (SD), mmHg	96 (13.1)	95 (13.0)	96 (13.2)	.95
Hypertension Control	626 (14.1)	300 (14.7)	326 (13.7)	.49
Heart rate, mean (SD), bpm	83 (13.6)	83 (13.5)	83 (13.7)	.16
Baseline treatment rate	4251 (96.0)	1990 (927.3)	2261 (95.0)	.25

Protocol 1- Free pill combination protocol; Protocol 2- Fixed-dose combination therapy.
[a]Including Arabic school, Islamic school, Bible school, or Technical/Vocational school.

which was no longer significant after accounting for clustering (cluster adjusted *p*-value = .29). These patterns were confirmed in the analysis of all patients' data who visited all PHCs randomized in the trial (Figure 1B). Distributions of blood pressure at baseline and 6 months follow-up are presented in Figures S3 and S4.

Figure 2A,B show the change in SBP and DBP from baseline to 6-month follow-up by treatment protocol group. There was a modest decline in SBP (1.46 mm Hg; 95% CI = −1.66 to 4.61) and DBP (.09 mm Hg; 95% CI = −1.70 to 1.89) for the two treatment protocols from baseline to 6 months (Table S3) with a corresponding increase in hypertension control (Figure S2).

Table 2 shows the adjusted odds ratio (adjOR) of cluster-adjusted hypertension control between Protocols 1 and 2 using multilevel generalized linear mixed-effect modeling for patients who visited their PHC at least twice. There was no difference in the adjOR of hypertension control from baseline to 6-month follow-up in the FDC group (Protocol 2) compared to the free pill group (Protocol 1), even after multivariable adjustment (adjusted OR [95% CI]: 1.07 [.73, 1.58]). There were also no differences in adjOR of hypertension control in the modeling using data from all patients in all randomized PHC (Table S4). A sensitivity analysis that included all patients who were treated in all PHCs sites after multiple imputations confirmed these patterns in treatment effects on hypertension control rate, changes in systolic BP and diastolic BP and the adjusted odds ratio (adjOR) of cluster-adjusted hypertension control.

3.3 | Secondary outcomes

Figure S5 shows the difference in hypertension treatment rates from baseline to 6-month follow-up. The proportion of patients treated in Steps 2 and 3 significantly increased for the two treatment protocols over the 6 months period. In Step 2, the proportion of patients treated with FDC combination at baseline was 17.2% and 30.4% at 6-month follow-up (*p*-value < .01) while the proportion of patients treated with free pill combination was 15.5 % at baseline and 26.9% at 6-month follow-up (*p*-value < .01). In Step 3, the proportion of patients treated with FDC combination at baseline was 3.5% and 6.2%

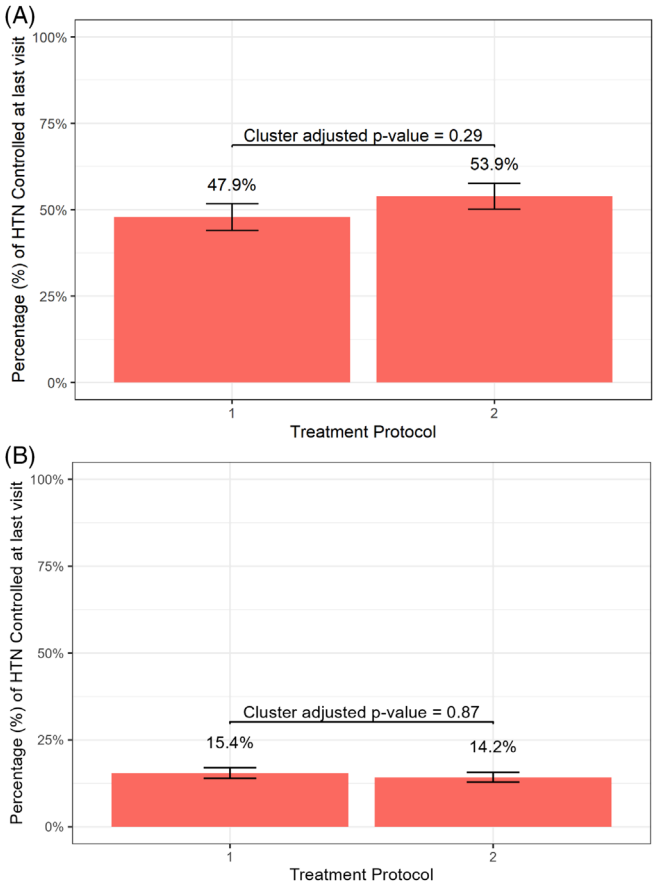

FIGURE 1 (A) Hypertension control rate (95% CI), defined as blood pressure <140/<90 mm Hg at the last visit by treatment protocol for patients who visited a primary healthcare center at least twice from baseline to 6 months. Protocol 1- Free pill combination protocol; Protocol 2- Fixed-dose combination therapy.
(B) Hypertension control rate (95% CI), defined as blood pressure <140/<90 mmHg at the last visit by treatment protocol for patients who visited a primary healthcare center at least twice from baseline to 6 months. Protocol 1- Free pill combination protocol; Protocol 2- Fixed-dose combination therapy.

at 6-month follow-up (p-value < .01) while the proportion of patients treated with free pills combination was 4.0% at baseline and 6.0% at 6-month follow-up (p-value = .01).

Hypertension control (95% CI), defined using a lower blood pressure target of <130/<80 mm Hg from baseline to 6-month follow-up, by calendar month stratified by treatment protocol, are provided in Figure S6. The hypertension control rate (defined by blood pressure <130/<80 mm Hg) at the last visit by treatment protocol among patients who had visited a PHC twice during the study period was similar for patients randomized to Protocol 1 and Protocol 2 (20.7% Vs. 24.1%, unadjusted p-value = .14). The results were of borderline statistical significance after accounting for clustering (cluster adjusted p-value = .052).

Figure S7 shows the between-group difference in time to hypertension control, defined as the time from blood pressure SBP ≥ 140 or DBP ≥ 90 mm Hg to <140/<90 mm Hg over the study period, and measured at the individual patient level. Median (interquartile range) time to hypertension control was similar between groups (Protocol 1: 4 (3) months versus Protocol 2: 4 (3) months, cluster adjusted p = .97).

TABLE 2 Multilevel generalized linear mixed models to evaluate the effect of treatment protocol on hypertension control from baseline to 6-month follow-up for patients who visited their PHC at least twice

	Adjusted OR (95%CI) for Hypertension control (blood pressure <140/<90 mm Hg)		
Treatment group	Model 1[a]	Model 2[b]	Model 3[c]
Protocol 1	Reference	Reference	Reference
Protocol 2	1.09 (.72, 1.64)	1.02 (.68, 1.53)	1.07 (.73, 1.58)
ICC (patient * PHC)	.44	.43	.43
ICC (PHC)	.06	.06	.05
ICC (visit time)	.01	.01	.01

Protocol 1- Free pill combination protocol; Protocol 2- Fixed-dose combination therapy.
Nested random effect: subject id in each site and crossed random effect (visit time in months for each patient in each site).
Abbreviations: BMI, body mass index; CI, confidence interval; ICC, intraclass correlation coefficient; OR, odds ratio; PHC, primary healthcare center.
[a]Adjusted for clusters (sites) and visit time as random effects.
[b]Adjusted clusters and visit time as random effects and age, and sex as fixed effects.
[c]Adjusted for clusters, and visit time as random effects and age, sex, BMI, alcohol use, education, heart rate, pre-existing hypertension or newly diagnosed as a fixed effect.

3.4 | Safety outcomes

Table 3 reports adverse events of patients during the study period. There was one death due to causes other than hypertension in Protocol 2 compared with none in Protocol 1. There were no unanticipated problems. Adverse events of special interest occurred in 20 patients (4 in Protocol 1; 16 in Protocol 2). The number of patients who reported dizziness was higher for patients who were randomized to Protocol 2 compared to Protocol 1 (13 vs. 2) whereas the number of patients who were hypotensive was higher in Protocol 1 compared to Protocol 2 (2 vs. 0). Other adverse events were rare and similar for the two treatment groups. On the other hand, hypokalemia was significantly higher among patients randomized to the free pill combination protocol compared to the FDC protocol (13.2% vs. 4.5%, cluster adjusted p-value <.01, Table 3).

4 | DISCUSSION

4.1 | Summary of results

This study examines the effectiveness and safety of a treatment protocol that uses FDC therapy for second and third steps of hypertension

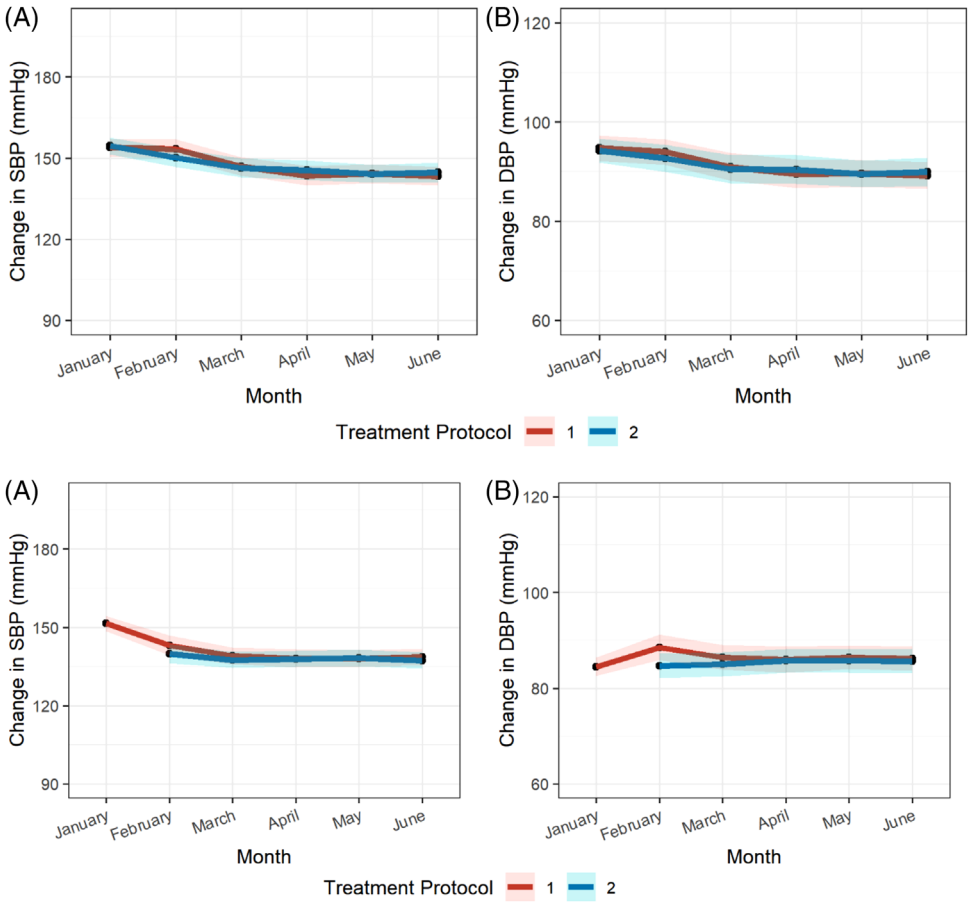

FIGURE 2 (A) Change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to 6-month follow-up, stratified by treatment protocol. (B) Change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to 6-month follow-up, stratified by treatment protocol for patients who visited their PHC at least twice.

therapy compared with free pill combination therapy among 60 public primary healthcare centers participating in the Hypertension Treatment in Nigeria Program. Even though patients who received the FDC therapy had numerically higher blood pressure control rate at 6 months compared to those who received the free pill combination (53.9% vs. 47.9%), this difference was not statistically significant after adjustment for clustering. Median time to hypertension control was 4 months, which was also similar for patients in the two treatment protocols. The number of adverse events reported was generally low in both groups; however, dizziness was more common among patients who received the FDC protocol (.5%) compared to patients who received the free pill combination protocol (.1%). On the other hand, hypokalemia was significantly higher among patients who received the free pill combination therapy compared with patients randomized to the FDC group.

4.2 | Results in context

Use of combination drugs is recommended by the hypertension guidelines issued in Nigeria,[13] as well as guidelines issued in the United States (if SBP > 20 mmHg),[21] in Europe (for most patients unless frail),[22] and by the World Health Organization in the *initial* treatment of hypertension because of its efficacy and cost-effectiveness in achieving blood pressure control more easily and more quickly compared with monotherapy. Treatment initiation with FDC therapy achieves better blood pressure control due to addressing 2 main barriers to long-term blood pressure control: low adherence and therapeutic inertia.[2,9] However, our study showed no significant difference in blood pressure control for patients who received the FDC therapy and those who received the free pill combination therapy when used in Step 2 or Step 3. Similarly, median time to achieve first BP control in this study was 4 months and this is quicker than what a previous retrospective cohort study in public PHC in Malaysia showed.[23] A plausible explanation for similar rates of blood pressure control and time to achieve first blood pressure control between the two treatment protocols may be because use of FDC in this study was initiated in Step 2 and not as the initial treatment. Previous studies have shown that use of FDC at the start of hypertension treatment (Step 1) may be better in achieving control than starting in Step 2.[21,22,24] The provision of free medications in a multi-level hypertension control program may have further attenuated potential between-group differences.

The similarity in blood pressure control and time to achieve first blood pressure control between the two treatment protocols may also be due to possible similarity in medication adherence in the two

TABLE 3 Adverse events of both treatment protocols in patients enrolled from baseline to 6-month follow-up

Adverse events, no. (%)	Treatment received		
Clinical adverse events	Protocol 1 ($n = 2046$)	Protocol 2 ($n = 2381$)	Cluster adjusted p-value
Cough	0 (.0)	1 (<.1)	–
Dizziness	2 (0.1)	13 (.5)	–
Swollen legs	0 (0)	1 (<.1)	–
Hypotension	2 (.1)	0 (0)	–
Death	0 (0)	1 (<.1)	–
Laboratory abnormalities[a]	**Protocol 1 ($n = 355$)**	**Protocol 2 ($n = 335$)**	
Serum sodium			.02
Abnormal	31 (8.7)	21 (6.3)	
Normal	324 (91.3)	313 (93.7)	
Serum potassium			<.01
Abnormal	47 (13.2)	15 (4.5)	
Normal	308 (86.8)	319 (95.5)	
Serum creatinine			.08
Abnormal	31 (11.7)	22 (8.0)	
Normal	234 (88.3)	253 (92.0)	

Protocol 1- Free pill combination protocol; Protocol 2- Fixed-dose combination therapy.

[a]Data were based on 5 sites randomly selected in each group based on staff strength and feasibility of on-site laboratory monitoring.

treatment groups. The lack of difference in blood pressure control and time to achieve first blood pressure control between the two treatment protocols in this study suggests that multilevel approach to hypertension treatment in this population will be needed to improve hypertension control beyond use of FDC alone. For instance, the HTN Program's multilevel hypertension treatment strategies, including hypertension registry, performance report, simplified treatment guidelines and patient care, and non-physician care, have demonstrated an increase from a 20% baseline control rate in January 2020 to 52% hypertension control rate as of December 2021. A systematic review of 100 randomized controlled trials has demonstrated that multilevel strategies are most effective for blood pressure control in patients with hypertension and should be used to improve hypertension control.[25]

Further, this study showed that the number of clinical adverse events in the two treatment protocols was generally low and similar between groups, apart from laboratory adverse events. This finding supports what other studies have shown that FDC therapy is safe.[10,26] Previous research showed that contemporary antihypertensive medications such as long-acting calcium channel blockers, angiotensin receptor blockers, and low dose thiazide diuretics reduce risks of adverse events compared with other drug classes,[27] which may also explain why adverse events were low in this study. Since FDC has benefits of increases in hypertension control, adherence, and potentially lower cost, it will be necessary to implement FDC into additional, multilevel hypertension treatment strategies in preventing complications of uncontrolled hypertension in Nigeria.

4.3 | Strengths and limitations

This cluster randomized trial was the first of its kind in Nigeria; however, it has also some limitations. First, adherence was not directly measured but the proportion of treated patients controlled was used as a proxy.[2] Second laboratory data on serum electrolytes, urea, and creatinine reported in this study were based on 10 PHCs who had the required staff strength to collect laboratory sample collections for analysis at a central laboratory. Third, the study evaluated protocol differences in second and third steps because of safety concerns with angiotensin receptor blockers at the first step. Upfront may be more effective and efficient to improve hypertension control, especially given the observed clinical inertia where only a minority of patients received Step 3 treatment and beyond, despite half of patients not having their blood pressure controlled at 6 months. Finally, this study was slightly underpowered. However, given the wide confidence interval we found in our analyses, it is unlikely we would have found a significant difference in the odds of control with a marginally larger or longer study.

5 | CONCLUSION

This study compared effectiveness and safety of protocols that used FDC and free pill combination in the second and third steps on hypertension control in the largest facility-based hypertension control program in Africa using a cluster randomized trial design. The study showed that there was no between-group difference in hypertension control. Since FDC therapy is part of the Nigerian hypertension treatment guidelines, it will be important for policy makers to develop pragmatic ways on how to improve access to its upfront use. FDC improves adherence to antihypertension medications and risk for hypertension-related complications in Nigeria.

AUTHOR CONTRIBUTIONS

Mark D. Huffman, Dike B. Ojji, Abigail S. Baldridge, Lisa R. Hirschhorn, Ikechukwu A. Orji, Gabriel L. Shedul, Eugenia N. Ugwuneji, Nonye Egenti, Kasarachi Omitiran, and Rosemary Okoli conceptualized and designed the study. Boni M. Ale performed the statistical data analysis and interpreted the results. Olutobi A. Sanuade and Boni M. Ale wrote the first draft of the manuscript. Olutobi A. Sanuade, Boni M. Ale Abigail S. Baldridge, Lisa R. Hirschhorn, Ikechukwu A. Orji, Gabriel L. Shedul, Eugenia N. Ugwuneji, Nonye Egenti, Kasarachi Omitiran, Rosemary Okoli, Helen Eze, Ada Nwankwo, Lisa R. Hirschhorn, Aashima Chopra, Jiancheng Ye, Priya Tripathi, Bolanle Banigbe, Namratha R. Kandula, Mark D. Huffman, and Dike B. Ojji provided critical revision of the manuscript for important intellectual content. Mark D. Huffman and Dike B. Ojji obtained funding for the study. All authors reviewed and approved the manuscript.

ACKNOWLEDGMENTS

We acknowledge the patients and teams at each of the 60 participating public primary health centers. We would like to thank members of the HTN Program investigators and advisory board who contributed to the planning and execution of this study, including: Dr Morenika Alex-Okoh, Dr Oyinlola Sanni, Dr. Mangai Toma, Dr. Nina Ezeigwe, Dr. Saddiq Abdurrahman, Dr. Isah Y. Vatsa, Dr. Mary Dewan, Mr. Michael Uwazie, Dr. Sunday Goji, PharmD Innocent Uche Nnubia, Dr. Ibrahim Katibi, and Dr. Emmanuel Agogo. We would like to thank members of the Data and Safety Monitoring Board who have overseen the conduct of this study, including: Dr. Brian Rayner (chair), Dr. Amam Mbakwem, Dr. Justine Davies, Dr. James Sheppard, Dr. Patricia Ojiah, Dr. Amanda Thrift, and Dr. Adeloye Davies.

CONFLICT OF INTEREST

MDH has pending patents for heart failure polypills. George Health Enterprises Pty Ltd (GH) and its subsidiary, George Medicines Pty Ltd, have received investment funds to develop fixed-dose combination products, including combinations of blood pressure-lowering drugs. GH is the social enterprise arm of The George Institute for Global Health. Other co-authors declare no conflicts of interest.

FUNDING STATEMENT

The study is supported by the National Heart, Lung, and Blood Institute (R01HL144708), Northwestern Robert J. Havey MD Institute for Global Health, and Resolve to Save Lives. The funders were not involved in the development of the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The program officer representing the National Heart, Lung, and Blood Institute participated in Data and Safety Monitoring Board activities. The Northwestern Robert J. Havey MD Institute for Global Health and Resolve to Save Lives contributed support for projects embedded within the overall HTN Program.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Sanuade OA, Ale BM, Baldridge AS, et al. Fixed-dose combination therapy-based protocol compared with free pill combination protocol: Results of a cluster randomized trial. *J Clin Hypertens*. 2023;25:127–136. https://doi.org/10.1111/jch.14632