Effectiveness and tolerability of Perindopril plus Amlodipine single pill combination in Nigeria: The 13 City Hypertension Study

Dike Ojji[1,2], Victor Ansa[3], Boni Ale[2], Mahmoud Sani[4], Austine Obasahan[5], Sola Alagbe[6], Rotimi Williams[7], Tony Aknitomide[8], Innocent Okoye[9], Ejiroghene Umuerri[10], Eze Nwafor[11], Amam Mbakwem[12], Casmir Amadi[12], Lamkur Shedu[2], Ranti Familoni[13], Taiwo Olunuga[14], Francisca Inofomoh[13], Ukachukwu Osuji[15], Godwin Omejua[16], Benjamin Azubuike[16], Esther Ohihoin[17] and Raphael Anakwe[18]

[1]Department of Internal Medicine, Faculty of Clinical Sciences, University of Abuja, Abuja, Nigeria
[2]Cardiovascular Research Unit, University of Abuja, Abuja, and University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria
[3]University of Calabar Teaching Hospital, Calabar, Nigeria
[4]Aminu Kano Teaching Hospital, Kano, Nigeria
[5]University of Benin Teaching Hospital, Benin-City, Nigeria
[6]General Hospital, Lagos Island, Lagos, Nigeria
[7]AMITEDA Hospital, Akure, Nigeria
[8]Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria
[9]Chukwu Emeka Odumegwu Ojukwu University Teaching Hospital, Nnewi, Nigeria
[10]Department of Internal Medicine, Faculty of Clinical Medicine, College of Health Sciences, Delta State University, Abraka, Nigeria
[11]University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria
[12]College of Medicine, University of Lagos, Lagos, Nigeria
[13]Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria
[14]Federal Medical Centre, Abeokuta, Ogun State, Nigeria
[15]Federal Medical Centre, Owerri, Imo State, Nigeria
[16]Nnamdi Azikiwe University Teaching Hospital Nnewi, Nigeria
[17]HICI Healthcare Specialist Clinic, Ltd, Lagos, Nigeria
[18]University of Nigeria Teaching Hospital, Enugu, Nigeria

Address for correspondence:
Dr Dike B. Ojji
Department of Internal Medicine
Faculty of Clinical Sciences
College of Health Sciences
University of Abuja Gwagwalada
Hospital Road
Gwagwalada
Abuja
Nigeria

Email:
dike.ojji@uniabuja.edu.ng

ABSTRACT

Background: There is no large-scale study that has shown the efficacy of single pill combination (SPC) anti-hypertensive medications in black African population. We therefore evaluated the blood pressure (BP) lowering efficacy and the tolerability of Perindopril plus Amlodipine SPC in black African patients.

Methods: It was a multi-centre, prospective, observational programme among hypertensive patients using different doses of Perindopril and Amlodipine. Primary endpoint was assessed as the change in mean sitting systolic and diastolic BPs from baseline to 3 months.

Results: 937 patients (55.7% female) were analysed, and the mean age was 56.4 ± 12.7 years. Systolic and diastolic BPs were significantly reduced by 17.3/9.4mmHg, 21.1/10.8mmHg mmHg and 24.6/12.7mmHg at 4, 8 and 12 weeks respectively compared to baseline value (p<0.0001). Dry cough was seen in 0.64% and angioedema 0.1% of the patients.

Conclusions: Perindopril plus Amlodipine SPC provided clinically meaningful BP reductions and is well tolerated in a black African population. SAHeart 2022;19:6-12

INTRODUCTION

Hypertension specifically contributes to the burden of heart disease, cerebrovascular disease, kidney failure and premature mortality and disability.[1,2] Hypertension is a global challenge with more than a quarter of the world's adult population (1 billion) having hypertension in 2000, and this is expected to increase to 29% (about 1.56 billion) by 2025.[3] In addition, hypertension disproportionately affects more people in low- and middle-income countries compared to the high-income countries.[3] In Nigeria, the burden of hypertension is high with a prevalence of about 28.9%.[4]

Treating hypertension has been associated with a 16% reduction in the risk of coronary heart disease and a 36% reduction in the risk of stroke, and several large clinical trials have demonstrated that more than one anti-hypertensive agent is usually needed to achieve target BP in majority of patients.[5-7] Consequently, current guidelines[8-14] recommend the use of combination therapy as first-line treatment or early in the management of hypertensive patients. Furthermore, contemporary guidelines on the management of hypertension also favour the use of single-pill combinations as they reduce the number of

tablets to be taken by the patient and therefore improve compliance with treatment.[8-12]

Whereas the benefits of combination therapy including single-pill combinations are obvious, and the best combination for the black African hypertensive patient has been described,[15] there is lack of large population studies in this group of patients that have studied the efficacy of contemporary single combination therapies, despite the high burden of hypertension and its complications in this population.[16-21]

We therefore decided to study the efficacy and tolerability of Perindopril/Amlodipine single-pill combination (COVERAM) on BP control in blacks residing in Nigeria. Although it is often argued that findings in African-Americans may be applied to black Africans since they have the same ancestral origin, the differences in selection in previous generations, ethnic admixture and differences in lifestyle suggest that such an extrapolation may not be appropriate.[22,23] There is therefore a need for studies in black hypertensive patients residing in sub-Saharan Africa.

METHODS

Study design

The 13 City Hypertension Study was a multicentre, prospective, observational programme among hypertensive patients with a 3 month follow-up, which was carried out in 19 public and private hospitals distributed throughout the 6 geopolitical regions of Nigeria between 1 April 2017 and 30 November 2018.

It was conducted as a non-interventional study, therefore study-specific patient visits, tests and monitoring were not imposed, and only data originating from routine clinical practice were collected. Therapy was prescribed according to clinician preference and on the prescribing pattern in Nigeria.

Study participants

The observational study was limited to hypertensive patients aged 30 - 79 years as most patients treated for hypertension in Nigeria fall within this age range. For homogeneity, the following patients were excluded from the study: patients with clinically defined congestive heart failure; those with clinical features of renal failure or with serum creatinine levels greater than 170µmol/l when measurement was available; patients with history of coronary heart disease including chronic stable angina and myocardial infarction or acute coronary syndrome; patients with a history of stroke or transient ischaemic attack; patients with known or suspected secondary hypertension; those with any other concomitant illness, physical or mental impairment that could interfere with their effective observation; pregnant women or those of child-bearing age not taking reliable contraception, and patients with a history of intolerance to any of the study medications.

Outcome measures

The primary efficacy end point was change in office systolic blood from baseline to final visit (12 weeks). Effectiveness of BP reduction was also assessed according to the proportion of patients with BP control defined as systolic BP less than 140mmHg systolic and diastolic BP less than 90mmHg achieved with this single-pill combination (SPC). Other outcome measures included percentage of patients achieving blood pressure control when COVERAM was combined with a diuretic (Indapamide 1.5mg or other thiazide or thiazide-like diuretics) or other anti-hypertensive treatments, incidence and the nature of adverse events with this SPC and effects of this SPC on metabolic and renal parameters when they are available.

Safety and tolerability were assessed by physician monitoring of adverse events (AEs) and serious AEs (SAEs), and assessment of the incidence and intensity of oedema.

STATISTICAL CONSIDERATIONS

Due to the observational nature of the study, descriptive statistical methods were used and supplemented by calculation of confidence intervals wherever this aided interpretation. The calculation of p-values was used either as an aid to evaluating a specific difference of interest, or as a "flagging" device applied to a large number of safety and tolerability efficacy variables to highlight differences worth further attention. This was particularly useful for laboratory data. Laboratory data were subjected to quantitative analysis. Patients enrolled in the programme with at least 1 follow-up visit or a documented adverse event were considered analysed.

We modelled systolic BP and diastolic BP using linear mixed models fitted with restricted maximum-likehood method which included adjustment for baseline BP, age (<55 or ≥55 years), gender, smoking status, body mass index (BMI) and subjects as a random effect.

All other patients were included in the evaluation even if they had partially missing data. We first constructed all models without accounting for missing data and secondly performed a sensitivity analysis. With the assumption that all were missing at random (MAR), we performed multiple-imputation analysis using chained equations. We generated 5 amputated data sets with a maximum of 1 000 iterations. Variables included in the imputation model were systolic BP and diastolic BP, age, gender, BMI, smoking status, including individuals. All analysis was performed with R Software 3.6.3 (The R Foundation for Statistical Computing platform).[24]

Ethical principles

The programme was conducted according to globally accepted standards of ISPE guidelines for good pharmaco-epidemiology practices.[25] The programme was conducted in compliance with national laws and regulations of Nigeria, as well as applicable guidelines.

All participating centres obtained approval from local institutional committees, and participating patients signed an informed consent in accordance with national and local regulations. The original dated and signed informed consent forms were retained by the investigator and a copy was given to the patient. For illiterate patients a caregiver read the document to the patient and took their verbal approval with the investigator as a witness. The caregiver signed on behalf of the patient stating that the patient was not literate.

Management of the study

The Steering Committee consisted of the principal investigator, the site investigators, the study statistician and the study pharmacist. This committee was chaired by the principal investigator.

TABLE 1: Demographic and clinical characteristics of the patients at baseline.

Variable	Value
Sex Female, number (%) Male, number (%)	 535 (57.1) 402 (42.9)
Age, years. SD	57.1 (12.6)
Background dyslipidaemia	138 (14.7)
Background diabetes mellitus	179 (19.1)
Cigarette habits, number (%) No smoking Stopped smoking Currently smoking	 850 (90.7) 71 (7.6) 16 (1.7)
Body mass index, kg/m^2	27.1 (8.9)
Systolic blood pressure, mmHg. SD	155.9 (18.6)
Diastolic blood pressure	92.9 (11.8)
Heart rate, beats per minute	81.7 (14.6)
Fasting blood sugar, mmol/l (number = 380)	5.2 (1.6)
Total cholesterol, mmol/l (number = 380)	4.9 (1.2)
LDL Cholesterol, mmol/l (number = 376)	3.0 (1.6)
HDL Cholesterol, mmol/l (number = 376)	1.5 (0.6)
Serum Potassium, mmol/l (number = 340)	3.9 (1.5)
Serum Creatinine, mmol/l (number = 367)	92.4 (15.9)

LDL = Low density lipoprotein, HDL = High density lipoprotein, SD = Standard deviation.

RESULTS

The first patient was enrolled 1 April 2016 and the last patient was enrolled 30 November 2017.

Patient demographics and baseline clinical characteristics of patients

Table 1 shows the demographic and clinical characteristics of the patients. Data of 937 patients of the 960 screened were analysed with 57.1% of these patients being females. Mean age, mean body mass index (BMI), mean systolic BP and mean diastolic BP were 56.4 (12.7) years, 27.1 (8.9)kg/m^2, 155.9 (18.6)mmHg and 92.9 (11.8)mmHg respectively. 7.6% of the patients previously smoked while 1.7% are current smokers. Mean fasting blood glucose was 5.2 (1.6)mmol/l in 380 patients that had their fasting blood sugar analysed while fasting. Low density lipoprotein cholesterol and high density lipoprotein cholesterol were 3.0 (1.6)mmol/l and 1.5 (0.60)mmol/l respectively in 376 patients that had these parameters analysed. Supplementary Figure 1 shows that 50% of the patients had no additional co-morbid risk factors for cardiovascular disease, 30.8% had 1 additional risk factor, 14.0% had 2 risk factors, 1% had 3 - 4 additional risk factors and 0.2% had 5 additional risk factors.

The 4 existing doses of Perindopril/Amlodipine in Nigeria, which are10/10, 5/10, 10/5 and 5/5mg, were prescribed. The most prescribed was the 10/10mg strength in 54.1% of cases, followed by the 5/5mg strength in 24.9% of cases, while the least prescribed was the 5/10mg strength in 11.4% of cases.

Unadjusted blood pressure reduction with Amlodipine plus Perindopril single pill combination

Figure 1 show unadjusted change in both systolic and diastolic BP over time. There was a significant unadjusted difference in both systolic and diastolic BP when values at baseline were compared with values at the 4th week, 8th week and 12th week. The highest unadjusted difference in both systolic and diastolic blood pressures were seen between baseline and 12th week with differences in systolic BP and diastolic BP of 24.6mmHg and 12.7mmHg respectively.

Adjusted blood pressure reduction with Amlodipine plus Perindopril single pill combination and associated factors

In a linear mixed model and after adjusting for age, gender, BMI and smoking status, the largest clinically significant reductions in systolic and diastolic blood pressures were between baseline and the 8th week with differences in systolic BP and diastolic BP of 21.5mmHg and 10.7mmHg respectively as shown in Figures 2A and 2B. Apart from the duration of treatment which was significantly associated with a greater reduction in systolic BP in response to study medication, age greater than 55 years

was significantly associated with increased systolic BP while both treatment duration and age greater than 55 years were significantly associated with greater reduction in diastolic BP in response to study medications. BMI was significantly associated with a greater reduction response in diastolic BP but its effect was not significant on systolic BP in response to study medications (Supplementary Figures 2A and 2B).

A sensitivity analysis that included all patients who were treated in all study sites after multiple imputation confirmed these patterns in treatment effects (Supplementary Tables 1A and 1B).

46.1% of the 812 patients observed at the second (4th week) visit had their BP controlled (<140/90mmHg). 60.2% of the

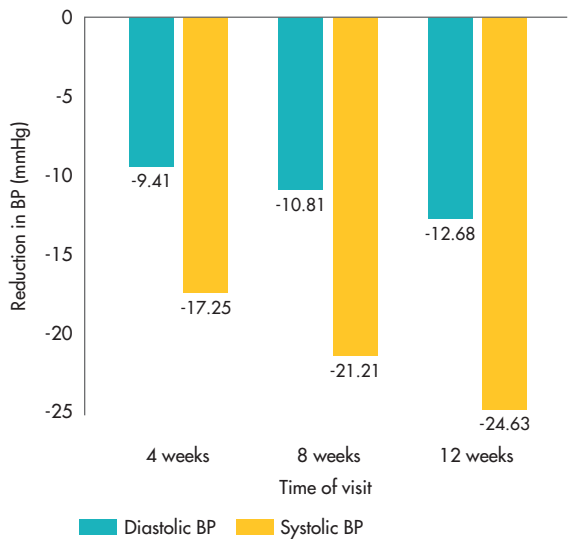


FIGURE 1: Mean difference reduction in Systolic and Diastolic BP over time.

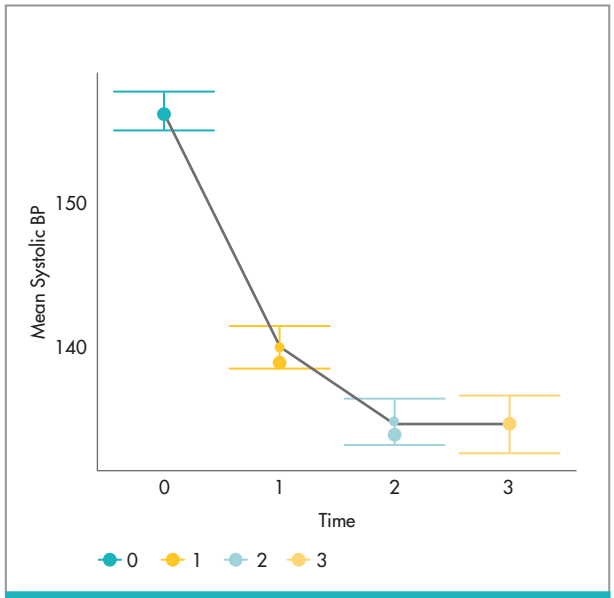
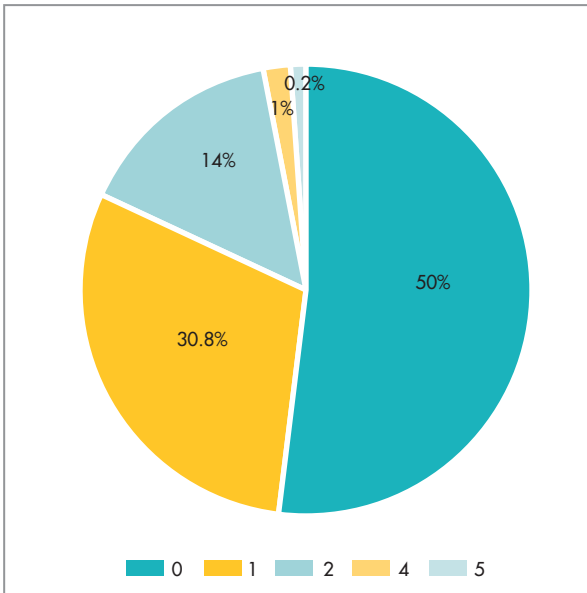


FIGURE 2A: Adjusted trend in Systolic BP from baseline to 12 weeks.
0 = baseline, 1 = 4 weeks, 2 = 8 weeks, 3 = 12 weeks.



SUPPLEMENTARY FIGURE 1: Percentage distribution of risk factors.

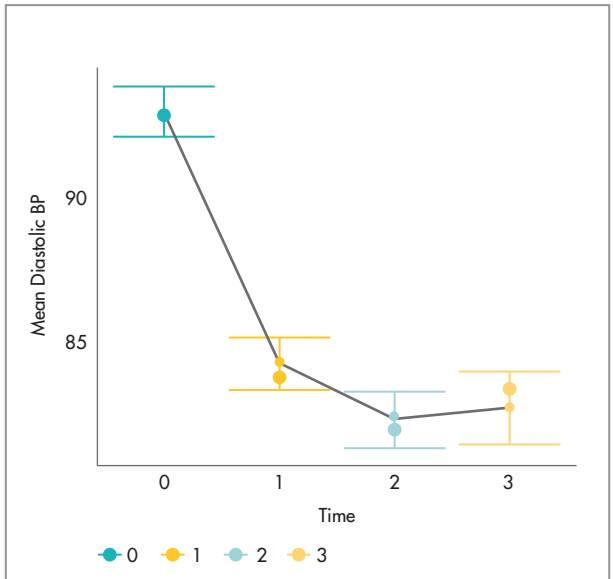


FIGURE 2B: Adjusted trend in Diastolic BP from baseline to 12 weeks.
0 = baseline, 1 = 4 weeks, 2 = 8 weeks, 3 = 12 weeks.

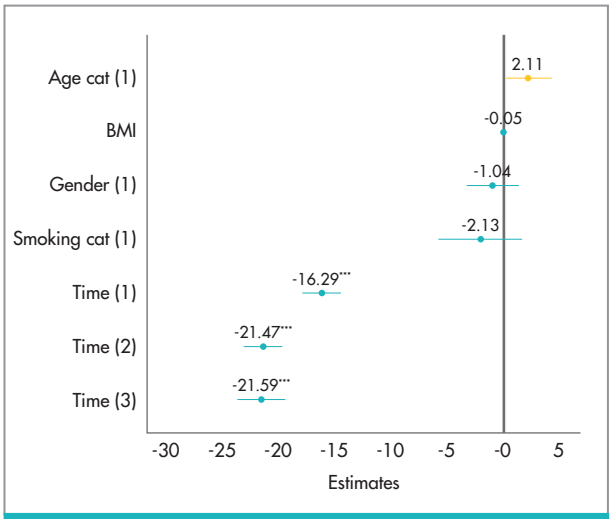
654 patients that came for third (8th week) visit had their BP<140/90mmHg. However, 9.8% of these patients needed an additional anti-hypertensive medication to control their blood pressure.

Safety and tolerability

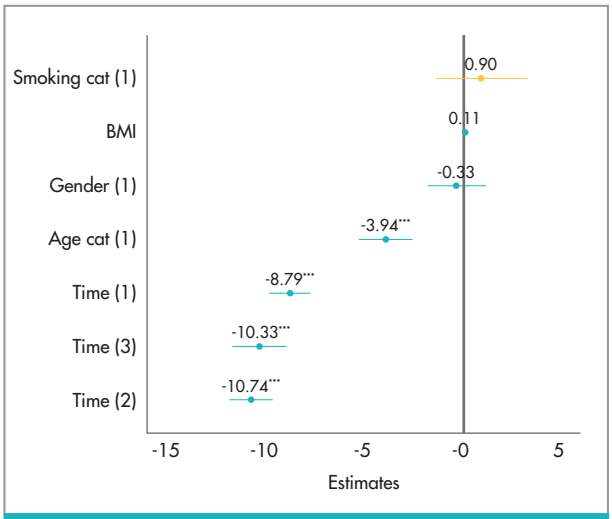
Table 2 shows that side effects of study medication were observed in 18 (1.9%) of the total number of patients studied with 14 (1.4%) stopping their study medications because of adverse events. Dry cough was the commonest side effect in 6 (0.6%) of the patients while angioedema occurred in only 1 (0.1%) of the patients.

Visit attendance rate and BP control

Table III shows the visit attendance rate and BP control. Clinic attendance dropped steadily over time. BP control was better at the 8th week compared to the 4th week.



SUPPLEMENTARY FIGURE 3A: Forest plot of factors influencing Systolic BP response to Amlodipine and Perindopril in treated patients.
*Smoking cat (1) = Former smokers + current smokers
*Time (1), (2), (3) = Time of visit 4 weeks, 8 weeks and 12 weeks
*Gender (1) = Female



SUPPLEMENTARY FIGURE 3B: Forest plot of factors influencing Diastolic BP response to Amlodipine and Perindopril in treated patients.
*Smoking cat (1) = Former smokers + current smokers
*Time (1), (2), (3) = Time of visit 4 weeks, 8 weeks and 12 weeks
*Gender (1) = Female

DISCUSSION

This is the largest anti-hypertensive observational study in black patients residing in sub-Saharan Africa in a real-world setting, and the results demonstrated that Amlodipine and Perindopril combinations significantly reduced both mean systolic and diastolic BPs compared to baseline over the study

SUPPLEMENTARY TABLE 1A: Sensitivity analysis, mean difference in Systolic BP after multiple imputations.

Term	Estimate	Standard error	P-value
Intercept	150.4	3.6	<0.001
4 weeks	-17.4	0.8	<0.001
8 weeks	-22.1	0.9	<0.001
12 weeks	-21.6	0.9	<0.001
Age	0.09	0.03	<0.001
Gender, Female	-0.7	0.9	0.48
BMI	0.01	0.1	0.88
Former Smoker	0.3	1.8	0.88
Current Smoker	-3.9	3.1	0.21

SUPPLEMENTARY TABLE 1B: Sensitivity analysis, mean difference in Diastolic BP after multiple imputations.

Term	Estimate	Standard error	P-value
Intercept	100.0	1.9	<0.001
4 weeks	-9.3	0.6	<0.001
8 weeks	-10.8	0.6	<0.001
12 weeks	-10.9	0.8	<0.001
Age	-0.2	0.02	<0.001
Gender, Female	-0.4	0.5	0.45
BMI	0.1	0.1	0.11
Former Smoker	1.2	0.1	0.23
Current Smoker	-1.5	2.3	0.51

TABLE II: Adverse event records in the 937 patients studied.

Nature of adverse event	Value, number (%)
Dry cough	6 (0.64)
Palpitations	2 (0.22)
Leg swelling	2 (0.22)
Dizziness	2 (0.22)
Chest pain	2 (0.22)
Headaches	1 (0.11)
Angioneuroedema, number	1 (0.11)
Others	4 (0.43)

Others = Generalised body weakness (1), generalised body pain (1), hyperpigmented papules (1), shortness of breathe (1).

TABLE III: Visit attendance rate and BP control.

	4 weeks	8 weeks	12 weeks
Visit attendance rate, n (%)	812 (84.6)	654 (68.1)	345 (35.9)
BP Control (<140/90mmHg) n (%)	374 (46.1)	394 (60.2)	

period. This further confirms the already demonstrated effectiveness of the combination therapy of Amlodipine and renin angiotensin aldosterone blockers in blacks residing in sub-Saharan Africa.[15,23] Overall, greater than half of all the patients observed reached the pre-defined therapeutic BP goal of less than 140/90mmHg with about 46% of those observed at 4 weeks reaching this goal, while 61.4% of those observed at 8 weeks reached the goal on single pill combination of Amlodipine and Perindopril. The levels of BP reduction seen in this study is similar to the values that have been previously reported in black Africans in response to the administration of combinations of Amlodipine with angiotensin converting enzyme inhibitors or angiotensin receptor blockers.[15,26]

Study duration and female gender were associated with greater reduction in systolic BP in response to study medication, while both age and female genders were associated with a greater response to diastolic BP in response to study medications. Similar findings have been reported and have been attributed to both hormonal changes and arterial stiffness in these patients.[27]

Amlodipine/Perindopril was generally well-tolerated in this patient population, with overall low rates of dry cough, pedal oedema, headaches and angioedema. The report of dry cough in about 0.6% and angioedema in 0.1% of those studied is much lower than those reported in African Americans in which dry cough occurred as much as in 3% - 5% of the patient population and angioedema occurred in about 1% - 2% of the cases.[28]

Similar to previous large hypertension observational studies in sub-Saharan Africa, a larger proportion of our patients (57.1%) were females, the patients were on the average overweight and the rate of smoking was low.[15] This larger proportion of females in hypertension studies might be attributed to better health-seeking behaviour and therefore better adherence to clinic attendance than males in our environment. It could be also attributed to earlier exposure to hypertension screening in female patients during antenatal care. Average body mass index of 29.9kg/m^2 might point to the effect of Westernisation and lifestyle changes in our population, and therefore calls for the need for mass education of our population on the need for lifestyle changes.[29,30]

One of the strengths of this study is that the observational design of the study has permitted the collection of a large amount of real-world data from different geopolitical regions of the world's largest black population which is more representative of the patient population encountered in routine clinical practice.

Analysing these data pooled from 17 cities across Nigeria, the 13 City Hypertension Study has contributed a significant body of data on the management of hypertension in sub-Saharan Africa.

This study has also helped in the collection of data from a lower middle income economy that is facing an increasing hypertension burden. Notably, useful data has been collected.

One of the main limitations of this study is the non-randomised, open-label design of this study as this has the potential of introducing observer bias. However, with the standardised methods for data collection we think this bias could have been greatly minimised. The large number of patients included could also have served in increasing the validity of this data.

CONCLUSION

The 13 City Hypertension Study has shown that Perindopril plus Amlodipine SPC is efficacious in clinically meaningful BP reductions and is well tolerated in a black African population in a real-world setting.

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