ORIGINAL ARTICLE

Comparison of Dual Therapies for Lowering Blood Pressure in Black Africans

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ABSTRACT

BACKGROUND

The prevalence of hypertension among black African patients is high, and these patients usually need two or more medications for blood-pressure control. However, the most effective two-drug combination that is currently available for blood-pressure control in these patients has not been established.

METHODS

In this randomized, single-blind, three-group trial conducted in six countries in sub-Saharan Africa, we randomly assigned 728 black patients with uncontrolled hypertension (≥140/90 mm Hg while the patient was not being treated or was taking only one antihypertensive drug) to receive a daily regimen of 5 mg of amlodipine plus 12.5 mg of hydrochlorothiazide, 5 mg of amlodipine plus 4 mg of perindopril, or 4 mg of perindopril plus 12.5 mg of hydrochlorothiazide for 2 months. Doses were then doubled (10 and 25 mg, 10 and 8 mg, and 8 and 25 mg, respectively) for an additional 4 months. The primary end point was the change in the 24-hour ambulatory systolic blood pressure between baseline and 6 months.

RESULTS

The mean age of the patients was 51 years, and 63% were women. Among the 621 patients who underwent 24-hour blood-pressure monitoring at baseline and at 6 months, those receiving amlodipine plus hydrochlorothiazide and those receiving amlodipine plus perindopril had a lower 24-hour ambulatory systolic blood pressure than those receiving perindopril plus hydrochlorothiazide (between-group difference in the change from baseline, −3.14 mm Hg; 95% confidence interval [CI], −5.90 to −0.38; P=0.03; and −3.00 mm Hg; 95% CI, −5.8 to −0.20; P=0.04, respectively). The difference between the group receiving amlodipine plus hydrochlorothiazide and the group receiving amlodipine plus perindopril was −0.14 mm Hg (95% CI, −2.90 to 2.61; P=0.92). Similar differential effects on office and ambulatory diastolic blood pressures, along with blood-pressure control and response rates, were apparent among the three groups.

CONCLUSIONS

These findings suggest that in black patients in sub-Saharan Africa, amlodipine plus either hydrochlorothiazide or perindopril was more effective than perindopril plus hydrochlorothiazide at lowering blood pressure at 6 months. (Funded by GlaxoSmithKline Africa Noncommunicable Disease Open Lab; CREOLE ClinicalTrials.gov number, NCT02742467.)

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†A complete list of the CREOLE investigators and committee members is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 18, 2019, and updated on March 22, 2019, at NEJM.org.

N Engl J Med 2019;380:2429-39.
DOI: 10.1056/NEJMoa1901113

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Increased blood pressure is the largest single contributor to the global burden of disease, leading to 10.4 million deaths in 2017.[1] Extensive data from randomized trials have shown that lowering blood pressure reduces cardiovascular morbidity and mortality.[2,3] Results from such trials[2,3] and population-based studies[4] indicate that most patients with hypertension require at least two antihypertensive agents if even conservative goals for blood pressure (<140/90 mm Hg) are to be reached. Consequently, hypertension guidelines have increasingly emphasized the likely need for at least two antihypertensive drugs. Indeed, the most recent European guidelines[5] recommend the use of two drugs as initial therapy for most patients. However, recommendations for which dual combinations should be used for black patients differ across three guidelines in the United States[6-8] and the latest guidelines in Europe,[5] reflecting the fact that there are insufficient data to differentiate among currently recommended combinations of drugs for black patients.[9]

In contrast, data are consistent in showing that diuretics or calcium-channel blockers are more effective as monotherapy than other drug classes among black patients with hypertension.[10-13] Consequently, the combination of a diuretic with a calcium-channel blocker has been recommended in some[6,7,14] (but not all[8]) recent guidelines.

Given the high prevalence and burden of hypertension and its complications in black populations,[15-17] we initiated the CREOLE (Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans) trial to evaluate the hypothesis that a calcium-channel blocker (amlodipine) plus a thiazide diuretic (hydrochlorothiazide) would produce more effective blood-pressure control than either a calcium-channel blocker plus an angiotensin-converting–enzyme (ACE) inhibitor (perindopril) or a diuretic plus an ACE inhibitor.

Methods

Trial Design and Oversight

From June 2017 through December 2017, we enrolled patients in this randomized, three-group clinical trial at 10 centers in six countries in sub-Saharan Africa. Details regarding the trial design have been published previously.[18] The protocol, which was approved by the institutional review board and ethics committee at each participating center, is available with the full text of this article at NEJM.org; all the patients provided written informed consent.

The trial was overseen by the steering committee, with day-to-day management coordinated by one of the principal investigators, the trial monitor, two pharmacists, the data manager, and the quality officer. The trial was designed by the three principal investigators. The data and safety monitoring committee conducted safety surveillance of all data collected at 2, 4, and 6 months. Data were recorded by the site investigators onto paper case-report forms, which were then transferred into the REDCap electronic database maintained by data managers at the University of Cape Town. The funder, GlaxoSmithKline Africa Noncommunicable Disease Open Lab, provided in-kind logistic and statistical support in the trial design but had no role in data collection and analysis or in the decision to submit the manuscript for publication. The trial drugs were donated by Aspen Pharmacare as part of an educational grant.

All the authors had access to the final results and vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. The first and last authors wrote the first draft of the manuscript, which was revised or approved by all the authors, who also assume responsibility for the accuracy of its content and the decision to submit the manuscript for publication. Analyses were performed by the trial statistician and an independent statistical advisor.

Population

Male or female black patients with hypertension between the ages of 30 and 79 years were eligible if they had not received previous treatment for hypertension and had a systolic blood pressure of 150 mm Hg to 179 mm Hg while seated during an office visit (office blood pressure) or if they had an office systolic blood pressure of 140 mm Hg to 159 mm Hg while receiving monotherapy. Patients were excluded if they had a history of cardiovascular disease or secondary hypertension or were pregnant. Detailed inclusion and exclusion criteria have been published previously.[18]

PROCEDURES

At baseline, all the patients had completed 24-hour ambulatory blood-pressure measurement (taken every 30 minutes) with the use of a validated device (Meditech monitor [ABPM-05 model] and Meditech blood-pressure cuff). They had also undergone three measurements of office blood pressure with the use of standard methods.[18,19] Patients were then assigned in a 1:1:1 ratio to one of the three treatment groups by means of electronic randomization, with stratification according to age (<55 years or ≥55 years) and site. The investigators were not aware of trial-group assignments (single-blind randomization), and even though the pills that were provided to the patients were not identical because of cost and logistic reasons, repackaging them in opaque packs minimized potential bias.

Patients were required to discontinue any previous antihypertensive medications without a washout period and began to receive a daily regimen of 5 mg of amlodipine plus 12.5 mg of hydrochlorothiazide, 5 mg of amlodipine plus 4 mg of perindopril, or 4 mg of perindopril plus 12.5 mg of hydrochlorothiazide. After 2 months, these doses were doubled to 10 and 25 mg, 10 and 8 mg, and 8 and 25 mg, respectively, unless patients had unacceptable side effects (e.g., postural dizziness, pedal edema, or dry cough) or the office systolic blood pressure was less than 100 mm Hg.

The 24-hour blood-pressure measurements were repeated at 6 months. Recordings with fewer than 80% of scheduled measurements were repeated. Patients were followed up at 2, 4, and 6 months, at which points sitting office blood-pressure measurements were repeated with the use of a validated, semiautomated oscillometric device (Omron M6 Comfort [HEM-7321-E]).[20] Fasting blood samples were drawn at baseline and at 6 months.

END POINTS

The primary end point was the mean change in the 24-hour ambulatory systolic blood pressure between baseline and 6 months, after adjustment for the baseline ambulatory systolic blood pressure. Secondary end points were the change at 6 months in the ambulatory diastolic blood pressure; the change in the mean daytime (9 a.m. to 9 p.m.) and nighttime (midnight to 6 a.m.) ambulatory blood pressure; the change in office blood pressure at 2, 4, and 6 months; the proportion of patients who had a controlled office blood pressure (<140/90 mm Hg) at 2, 4, and 6 months (based on the mean of the second and third readings); the proportion of patients who had a response to treatment (defined as a reduction in the office blood pressure of >20 mm Hg systolic and >10 mm Hg diastolic) at 2, 4, and 6 months; and changes in blood analytes, pulse rates, and adverse events.

STATISTICAL ANALYSIS

The sample size of 702 patients was based on the detection of a minimal clinically important difference of 3.0 mm Hg in the ambulatory systolic blood pressure on the assumption of a standard deviation of 9.0 mm Hg.[21] To allow for a 10% dropout rate, we required the enrollment of 210 patients who could be evaluated in each group so that the trial would have a power of at least 84% at a significance level of 0.05, using a conservative adjustment for the three comparisons. Since the P values are not adjusted for multiple comparisons among the three groups, the values should be interpreted in the context of the planned P value threshold of 0.017 (0.05÷3) after Bonferroni adjustment.

For the primary end point, we used a linear mixed-effects model to estimate the mean difference in the ambulatory systolic blood pressure between the groups. We used the restricted maximum-likelihood method to fit the model, which included adjustment for the baseline ambulatory systolic blood pressure, age (<55 or ≥55 years), and trial site as a random effect.

Two sensitivity analyses were performed. First, in order to increase the precision of the estimate of the treatment effect, we adjusted the model for clinically important and other variables: sex, the presence of diabetes or dyslipidemia (total cholesterol, >5.2 mmol per liter [200 mg per deciliter] or the receipt of statins), body-mass index (BMI), pulse rate, and duration of hypertension. Second, we performed multiple-imputation analyses using chained equations for patients who had a missing primary end-point value. We generated five imputed-data sets with a maximum number of 1000 iterations, with linear imputation for continuous variables and logistic or multinomial regression for categorical vari-

ables. Variables that were included in the imputation model were treatment group, ambulatory systolic and diastolic blood pressures, office blood pressure measurements, age, sex, trial site, BMI, presence of diabetes or dyslipidemia, duration of hypertension, and pulse rate. We used the same framework to analyze ambulatory systolic and diastolic blood pressures.

The mean between-group difference in office blood pressure was estimated for each time point with the use of a linear mixed-effects model that included the patient as a random effect, along with age, baseline office blood pressure, follow-up duration, and interaction between time and treatment. We used logistic-regression analysis to compare the between-group response rate in office blood pressure after adjustment for age and site. All estimates of treatment effect were calculated with a 95% confidence interval. We used P values interpreted as a continuous measure to evaluate the strength of the evidence against the null hypothesis of no between-group difference.

We did not plan for multiple-comparison adjustments for secondary outcomes, so the results are reported with point estimates and 95% confidence intervals only. The widths of the confidence intervals have not been adjusted for multiple comparisons, which should be taken into consideration when interpreting these results.

We performed an efficacy analysis using the intention-to-treat principle and included all the patients for whom primary end-point data were available. Adverse events were assessed in all the patients until the end of follow-up and were tabulated according to trial group. All analyses were performed with Stata software, version 15 (StataCorp), and SPSS software, version 20 (IBM). The statistical methods are detailed in the Supplementary Appendix, available at NEJM.org.

RESULTS

PATIENTS

During the enrollment period, 890 patients underwent screening, and 728 were assigned to one of three study groups: 244 to the group receiving amlodipine plus hydrochlorothiazide, 243 to the group receiving amlodipine plus perindopril, and 241 to the group receiving perindopril plus hydrochlorothiazide.

Of these patients, 698 (95.9%) completed the trial; 621 (85.3%) underwent ambulatory blood-pressure monitoring at baseline and at 6 months. Of the 107 patients who did not undergo ambulatory blood-pressure monitoring at 6 months, 22 withdrew consent before or after starting other medications, 16 were lost to follow-up, 3 were excluded for protocol violations, and 66 declined to undergo monitoring at 6 months (Fig. S1 in the Supplementary Appendix).

The primary analysis included the 621 patients for whom data regarding ambulatory blood-pressure monitoring at 6 months were available. There were no important differences in baseline characteristics between the 621 patients who were included in the primary analysis and the 107 patients who were not included (Table S1 in the Supplementary Appendix). The 621 patients had a mean (±SD) age of 51.1±10.6 years, and 63.3% were women (Table 1).

BASELINE BLOOD-PRESSURE MEASUREMENTS

At baseline, office blood pressures were similar in the three treatment groups, but the mean ambulatory systolic blood pressure was highest in the group that received amlodipine plus perindopril (147.6±16.5 mm Hg, as compared with 145.6±14.6 mm Hg in the group that received amlodipine plus hydrochlorothiazide and 146.0±15.7 mm Hg in the group that received perindopril plus hydrochlorothiazide) (Table 1).

EFFECT OF TREATMENT COMBINATIONS ON AMBULATORY BLOOD PRESSURE

After 6 months, the unadjusted reductions in ambulatory systolic blood pressure from baseline were larger in the group that received amlodipine plus perindopril (18.1 mm Hg) and the group that received amlodipine plus hydrochlorothiazide (17.1 mm Hg) than in the group that received perindopril plus hydrochlorothiazide (14.2 mm Hg) (Fig. S2 in the Supplementary Appendix).

After adjustment for stratification variables and the baseline ambulatory systolic blood pressure, patients who received either of the two amlodipine combinations had a larger mean reduction in the ambulatory systolic blood pressure than those who received perindopril plus hydrochlorothiazide. As compared with the last group, the between-group difference in the change from baseline was −3.14 mm Hg (95% confidence interval [CI], −5.90 to −0.38; P=0.03) for amlodi-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Amlodipine–HCTZ (N=216)	Amlodipine–Perindopril (N=205)	Perindopril–HCTZ (N=200)
Sex — no. (%)			
Male	80 (37.0)	77 (37.6)	71 (35.5)
Female	136 (63.0)	128 (62.4)	129 (64.5)
Age			
Mean — yr	51.2±10.9	50.9±10.8	50.9±10.2
Distribution — no. (%)			
≥55 yr	84 (38.9)	74 (36.1)	72 (36.0)
<55 yr	132 (61.1)	131 (63.9)	128 (64.0)
Body-mass index†	28.7±5.5	28.5±5.7	27.8±6.1
Blood pressure — mm Hg			
Office			
Systolic	158.0±11.0	158.0±11.1	158.3±13.0
Diastolic	98.3±10.4	97.3±10.6	97.2±10.0
Ambulatory			
Systolic	145.6±14.6	147.6±16.5	146.0±15.7
Diastolic	88.3±10.5	90.0±11.9	88.3±10.4
Pulse — beats/min	83.3±13.8	80.1±13.7	81.8±14.0
Diabetes mellitus — no. (%)	5 (2.3)	12 (5.9)	18 (9.0)
Previous antihypertensive therapy — no. (%)			
Calcium-channel blocker	34 (15.7)	39 (19.0)	34 (17.0)
Diuretic	22 (10.2)	22 (10.7)	18 (9.0)
ACE inhibitor	5 (2.3)	9 (4.4)	8 (4.0)
ARB	4 (1.9)	2 (1.0)	6 (3.0)
Beta-blocker	1 (0.5)	1 (0.5)	1 (0.5)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and HCTZ hydrochlorothiazide.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

pine plus hydrochlorothiazide and −3.00 mm Hg (95% CI, −5.81 to −0.20 mm Hg; P=0.04) for amlodipine plus perindopril (Table 2). The difference between the group receiving amlodipine plus hydrochlorothiazide and the group receiving amlodipine plus perindopril was −0.14 mm Hg (95% CI, −2.90 to 2.61; P=0.92). Similar patterns in results were observed in comparisons in the mean 12-hour daytime and nighttime ambulatory systolic blood pressure.

After further adjustment for clinically important baseline variables, mean differences in effect estimates increased. As compared with perindopril plus hydrochlorothiazide, treatment with amlodipine plus hydrochlorothiazide resulted in a between-group difference of −3.57 mm Hg (95% CI, −6.31 to −0.83; P=0.01) in the mean ambulatory systolic blood pressure and −4.31 mm Hg (95% CI, −7.28 to −1.33) in the nighttime ambulatory systolic blood pressure; the corresponding between-group differences for amlodipine plus perindopril were −3.20 mm Hg (95% CI, −5.95 to −0.46) and −3.67 mm Hg (95% CI, −6.64 to −0.69), respectively (Table 2).

A sensitivity analysis that included all the patients who had undergone randomization after multiple imputation confirmed these differential treatment effects for both groups that received amlodipine combinations as compared with the group that received perindopril plus hydrochlo-

Table 2. Adjusted Mean Between-Group Differences in Changes from Baseline in Ambulatory Blood Pressure.*

Ambulatory Blood Pressure	Amlodipine–HCTZ vs. Perindopril–HCTZ		Amlodipine–HCTZ vs. Amlodipine–Perindopril		Amlodipine–Perindopril vs. Perindopril–HCTZ	
	Mean Difference (95% CI)	P Value	Mean Difference (95% CI)	P Value	Mean Difference (95% CI)	P Value
	mm Hg		*mm Hg*		*mm Hg*	
Model 1†						
24-hour						
Systolic	−3.14 (−5.90 to −0.38)	0.03	−0.14 (−2.90 to 2.61)	0.92	−3.00 (−5.81 to −0.20)	0.04
Diastolic	−1.05 (−2.67 to 0.55)		−0.41 (−2.01 to 1.18)		−0.64 (−2.27 to 0.98)	
12-hour						
Systolic						
Daytime	−1.93 (−4.75 to 0.89)		0.63 (−2.17 to 3.44)		−2.56 (−5.42 to 0.30)	
Nighttime	−3.79 (−6.80 to −0.78)		−0.41 (−3.38 to 2.56)		−3.38 (−6.43 to −0.33)	
Diastolic						
Daytime	−0.76 (−2.50 to 0.98)		−0.21 (−1.95 to 1.52)		−0.55 (−2.31 to 1.21)	
Nighttime	−1.52 (−3.22 to 0.17)		−0.69 (−2.36 to 0.98)		−0.83 (−2.55 to 0.89)	
Model 2‡						
24-hour						
Systolic	−3.57 (−6.31 to −0.83)	0.01	−0.37 (−3.09 to 2.35)	0.79	−3.20 (−5.95 to −0.46)	0.02
Diastolic	−1.37 (−2.97 to 0.23)		−0.63 (−2.22 to 0.96)		−0.74 (−2.34 to 0.86)	
12-hour						
Systolic						
Daytime	−2.52 (−5.30 to 0.24)		0.24 (−2.52 to 3.00)		−2.77 (−5.55 to 0.01)	
Nighttime	−4.31 (−7.28 to −1.33)		−0.64 (−3.56 to 2.28)		−3.67 (−6.64 to −0.69)	
Diastolic						
Daytime	−1.13 (−2.87 to 0.61)		0.49 (−2.23 to 1.24)		−0.64 (−2.38 to 1.11)	
Nighttime	−1.86 (−3.56 to −0.16)		−0.89 (−2.56 to 0.78)		−0.96 (−2.67 to 0.73)	

* The primary end point was the change in the 24-hour ambulatory systolic blood pressure between baseline and 6 months. Since the P values are not adjusted for multiple comparisons among the three groups, the values should be interpreted in the context of the planned P value threshold of 0.017 (0.05÷3) after Bonferroni adjustment.

† Model 1 was adjusted for stratification variables (age [<55 years or ≥55 years] and trial site) and the ambulatory systolic blood pressure at baseline.

‡ Model 2 was a sensitivity analysis adjusted for the stratification variables (age and trial site), baseline ambulatory systolic blood pressure, sex, presence of diabetes mellitus or dyslipidemia, body-mass index, heart rate, and duration of hypertension.

rothiazide (Table S2 in the Supplementary Appendix).

EFFECT OF TREATMENT COMBINATIONS ON OFFICE BLOOD PRESSURE

As compared with the group that received perindopril plus hydrochlorothiazide, the patients who received amlodipine plus hydrochlorothiazide had greater reductions in office systolic blood pressure at 2, 4, and 6 months, with a between-group difference at 6 months of −7.15 mm Hg (95% CI, −10.25 to −4.06) (Table 3). Patients who received amlodipine plus perindopril also had greater reductions in systolic blood pressure than did those who received perindopril plus hydrochlorothiazide at 4 and 6 months. At 2 months, the group that received amlodipine plus hydrochlorothiazide had a greater reduction in systolic blood pressure than the group that received amlodipine plus perindopril (between-group difference, −5.14 mm Hg; 95% CI, −8.30 to −1.74); however, at 4 months and 6 months,

Table 3. Adjusted Mean Between-Group Differences in Changes from Baseline in Office Blood Pressure.*

Office Blood Pressure	Amlodipine–HCTZ vs. Perindopril–HCTZ	Amlodipine–HCTZ vs. Amlodipine–Perindopril	Amlodipine–Perindopril vs. Perindopril–HCTZ
		Mean Difference (95% CI)	
		mm Hg	
Systolic			
2 Mo	−5.72 (−9.14 to −2.30)	−5.14 (−8.30 to −1.74)	−0.58 (−3.84 to 2.65)
4 Mo	−4.76 (−7.88 to −1.63)	−0.04 (−3.14 to 3.07)	−4.72 (−7.88 to −1.56)
6 Mo	−7.15 (−10.25 to −4.06)	−1.61 (−4.69 to 1.47)	−5.55 (−8.69 to −2.41)
Diastolic			
2 Mo	−3.49 (−5.49 to −1.49)	−2.81 (−4.79 to −0.82)	−0.68 (−2.71 to −1.34)
4 Mo	−2.39 (−4.24 to −0.53)	−0.14 (−1.70 to 1.98)	−2.53 (−4.23 to −0.53)
6 Mo	−4.86 (−6.84 to −2.89)	−1.27 (−3.23 to 0.70)	−3.60 (−5.60 to −1.60)

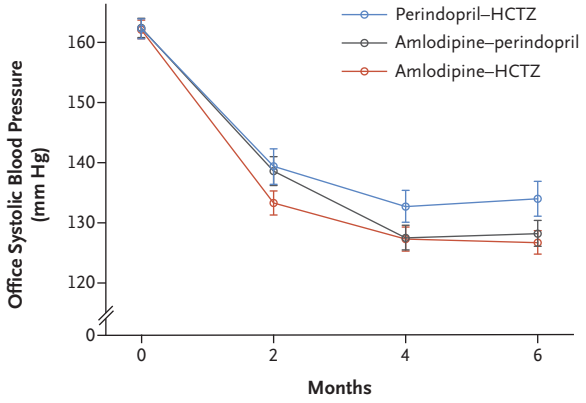
* The change in office blood pressure at 2, 4, and 6 months was one of the main secondary end points of the trial. The data were adjusted for randomization stratification variables (age [<55 years or ≥55 years] and site) and baseline ambulatory systolic blood pressure.

the between-group differences were smaller (−0.04 mm Hg and −1.61 mm Hg, respectively). Similar patterns in office diastolic blood pressure were observed across the three treatment groups. The response of office blood pressure to the three treatment combinations at each time point is shown in Figure 1.

On the basis of office blood pressures, the response rate at 2 months was higher in the group that received amlodipine plus hydrochlorothiazide than in the group that received amlodipine plus perindopril by 6.7 percentage points (95% CI, −1.8 to 15.1). However, by 4 and 6 months, a higher percentage of patients had a response to treatment in both of the amlodipine-combination groups than in the group that received perindopril plus hydrochlorothiazide (Table 4). Differences in control rates for blood pressure reflected those in response rates across the three groups over time.

EFFECT OF TREATMENT COMBINATIONS ON LABORATORY MEASURES AND PULSE RATES

The mean level of serum potassium was similar (4.2 mmol per liter) in all three groups at baseline but was lower at 6 months in the group that received amlodipine plus hydrochlorothiazide than in the group that received amlodipine plus perindopril and the group that received perindopril plus hydrochlorothiazide (3.8±0.45 mmol per liter, 4.1±0.44 mmol per liter, and 4.0±0.45 mmol per liter, respectively) (Table S3 in the Supplementary Appendix). At 6 months, the mean level of serum creatinine was higher in the group that received perindopril plus hydrochlorothiazide than in the two groups that received amlodipine combinations. There were no other important changes in biochemical variables at 6 months or



No. at Risk

Perindopril–HCTZ	224	224	214	204
Amlodipine–perindopril	225	225	214	207
Amlodipine–HCTZ	231	231	224	223

Figure 1. Office Systolic Blood Pressure during the Trial Period.

The office systolic blood pressure was measured at baseline and at 2, 4, and 6 months among the patients in the three trial groups who received perindopril plus hydrochlorothiazide (HCTZ), amlodipine plus perindopril, or amlodipine plus hydrochlorothiazide.

Table 4. Rates of Response and Control in Office Blood Pressure.

Variable	Amlodipine–HCTZ vs. Perindopril–HCTZ			Amlodipine–HCTZ vs. Amlodipine–Perindopril			Amlodipine–Perindopril vs. Perindopril–HCTZ		
	Amlodipine–HCTZ (N=216)	Perindopril–HCTZ (N=200)	Difference (95% CI)	Amlodipine–HCTZ (N=216)	Amlodipine–Perindopril (N=205)	Difference (95% CI)	Amlodipine–Perindopril (N=205)	Perindopril–HCTZ (N=200)	Difference (95% CI)
	no. (%)		*percentage points*	*no. (%)*		*percentage points*	*no. (%)*		*percentage points*
Response rate*									
2 mo	66 (30.6)	52 (26.0)	4.0 (−4.1 to 13.1)	66 (30.6)	49 (23.9)	6.7 (−1.8 to 15.1)	49 (23.9)	52 (26.0)	−2.1 (−6.3 to 10.5)
4 mo	176 (81.5)	147 (73.5)	7.9 (−0.0 to 3.7)	176 (81.5)	164 (80.0)	1.5 (−6.0 to 9.1)	164 (80.0)	147 (73.5)	6.5 (−1.7 to 14.7)
6 mo	177 (81.9)	140 (70.0)	11.9 (3.7 to 20.0)	177 (81.9)	164 (80.0)	1.9 (−5.6 to 9.4)	164 (80.0)	140 (70.0)	10.0 (1.6 to 18.3)
Control rate†									
2 mo	116 (53.7)	102 (51.0)	2.7 (−6.9 to 12.2)	116 (53.7)	86 (42.0)	11.7 (2.2 to 21.0)	86 (42.0)	102 (51.0)	−9.0 (−0.7 to 18.5)
4 mo	167 (77.3)	144 (72.0)	5.3 (−3.1 to 13.6)	167 (77.3)	162 (79.0)	−1.7 (−6.2 to 9.5)	167 (77.3)	144 (72.0)	5.3 (−3.2 to 13.7)
6 mo	164 (75.9)	120 (60.0)	15.9 (6.9 to 24.6)	164 (75.9)	151 (73.7)	2.2 (−6.1 to 10.5)	151 (73.7)	120 (60.0)	13.7 (4.5 to 22.6)

* The response rate is the proportion of patients with a reduction in the office systolic blood pressure of more than 20 mm Hg and a reduction in the office diastolic blood pressure of more than 10 mm Hg over a given time.
† The control rate is the proportion of patients with an office blood pressure of less than 140/90 mm Hg over a given time.

pulse rates at 2, 4, or 6 months among the three groups.

ADHERENCE AND ADVERSE EVENTS

Adherence to the trial regimen, as measured by pill counts, and rates of adverse events were similar in the three treatment groups (Table 5). Overall incident adverse events occurred in 14.6% of the patients, with only 5 patients discontinuing their medications because of adverse events. Hypokalemia (potassium level, <3.2 mmol per liter) was found in 5.3% of patients in the group that received amlodipine plus hydrochlorothiazide. As expected, cough was observed in association with the use of perindopril and pedal edema with the use of amlodipine. Angioedema was observed in association with perindopril in 5 patients.

DISCUSSION

In this randomized trial of three commonly recommended two-drug combinations of antihypertensive agents[5-7,14] involving black patients in sub-Saharan Africa, we found that the combinations of amlodipine with either hydrochlorothiazide or perindopril were more effective than perindopril plus hydrochlorothiazide in reducing both ambulatory systolic blood pressure and office blood pressure. The treatment response and control rates were also lower in the group that received perindopril plus hydrochlorothiazide. Our results suggest that a long-acting dihydropyridine calcium-channel blocker (in this case, amlodipine) may be critical to more efficacious blood-pressure lowering among black patients as part of the two-drug combinations used here. These results contrast with recommendations for black patients in the most recent U.S. guidelines,[8] which advise the use of either a calcium-channel blocker or a diuretic in combination with a different drug class. The findings also contrast with European guidelines,[5] which recommend the use of a combination of a calcium-channel blocker with a diuretic or with an ACE inhibitor or a combination of an ACE inhibitor with a diuretic.

The efficacy of calcium-channel blockers as monotherapy in black patients is well established.[10-13] Of note, the 24-hour blood-pressure–lowering efficacy of amlodipine has been linked to its long half-life of 48 to 72 hours,[22] a finding that is supported by the lower nighttime levels

Table 5. Adverse Events (Safety Population).*

Adverse Event	Amlodipine–HCTZ (N=244)	Amlodipine–Perindopril (N=243)	Perindopril–HCTZ (N=241)	All Patients (N=728)
	number of patients (percent)			
Any adverse event	39 (16.0)	39 (16.0)	28 (11.6)	106 (14.6)
Dry cough	0	14 (5.8)	12 (5.0)	26 (3.6)
Pedal edema	10 (4.1)	9 (3.7)	1 (0.4)	20 (2.7)
Palpitations	5 (2.0)	7 (2.9)	1 (0.4)	13 (1.8)
Headache	5 (2.0)	4 (1.6)	2 (0.8)	11 (1.5)
Angioedema	0	2 (0.8)	3 (1.2)	5 (0.7)
Dizziness	4 (1.6)	1 (0.4)	4 (1.7)	9 (1.2)
Hypokalemia†	13 (5.3)	1 (0.4)	4 (1.7)	18 (2.5)
Death	0	0	0	0
Other‡	2 (0.8)	1 (0.4)	1 (0.4)	4 (0.5)

* The safety population included all 728 patients who had undergone randomization. Rates of adherence to the trial regimens (as measured by pill counts) were 80.6% in the group that received amlodipine plus HCTZ, 79.8% in the group that received amlodipine plus perindopril, and 79.5% in the group that received perindopril plus HCTZ.
† Hypokalemia was defined as a serum potassium level of less than 3.2 mmol per liter.
‡ Other adverse events included erectile dysfunction, fainting, and frequent urination.

of ambulatory systolic blood pressure in the two amlodipine-combination groups in this trial. Furthermore, the efficacy of amlodipine in reducing blood pressure and cardiovascular events has been partly attributed to its effect on enhancing the bioavailability of vascular endothelial nitric oxide levels.[23] This factor may be particularly relevant to blood-pressure reduction in black patients with hypertension because this population is reported to have lower bioavailability of nitric oxide than white patients.[24,25]

On the basis of the preferential blood-pressure–lowering efficacy of diuretics and calcium-channel blockers as monotherapy in black patients,[10-13] we hypothesized that amlodipine plus hydrochlorothiazide would be the most effective of the three combinations in reducing the ambulatory systolic blood pressure. However, amlodipine plus perindopril was similarly effective in reducing both the ambulatory systolic blood pressure and the office blood pressure. Previous studies have shown that the hemodynamic effects of long-acting calcium-channel blockers and ACE inhibitors are complementary.[26,27] Furthermore, in the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial[28] and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial),[29] the combination of a calcium-channel blocker and an ACE inhibitor was associated with significantly better cardiovascular protection than an ACE inhibitor plus a thiazide or a beta-blocker plus a thiazide, respectively.

At 6 months, significant reductions in plasma potassium and higher rates of hypokalemia were present in the group that received amlodipine plus hydrochlorothiazide, which is surprising, given the low hydrochlorothiazide dose. Whether this finding reflects the low rate of consumption of fruit and vegetables in this population[30] merits further investigation. Small but nonsignificant increases in levels of fasting blood glucose and low-density lipoprotein cholesterol and a reduction in high-density lipoprotein cholesterol were also apparent in the group that received amlodipine plus hydrochlorothiazide, a finding that was consistent with the established metabolic effects of low-dose thiazides.[31] These small adverse metabolic effects, particularly on potassium levels, may offset some of the cardiovascular benefits of the observed additional blood-pressure lowering. Similarly, the rates of angioedema (1%) among those taking perindopril and of ankle edema (4%) among those taking amlodipine need to be considered when choosing between the two regimens that lowered blood pressures more effectively.

Limitations of the present trial include the

use of nonmatching trial drugs, although the packaging and delivery to patients ensured that the administration of the drugs was carried out essentially in a double-blind manner.[18] Since the P values for the three comparisons of the primary end point were not adjusted for multiple comparisons, the conclusions must be interpreted with caution. In addition, it is uncertain whether these data can be extrapolated to black patients with diabetes or those outside sub-Saharan Africa or whether the results necessarily pertain to the use of other agents in the same drug classes or to the use of thiazide-like rather than thiazide diuretics.[32] Thiazide-like diuretics are more effective blood-pressure–lowering agents[32] and have more evidence indicating that they prevent adverse cardiovascular events[33] than low-dose thiazides. However, the latter agents are the commonest diuretics used worldwide and in sub-Saharan Africa, where they are also much cheaper and more easily available. Hence, hydrochlorothiazide was used in this trial. Nevertheless, it remains possible that the effects on blood-pressure lowering observed in this trial might have differed if a thiazide-like diuretic had been used.

In conclusion, in this trial involving black patients in sub-Sahara Africa, we found that among three commonly recommended drug combinations, amlodipine (a long-acting dihydropyridine calcium-channel blocker) combined with either an ACE inhibitor (perindopril) or a thiazide diuretic (hydrochlorothiazide) was superior to perindopril plus hydrochlorothiazide in lowering both ambulatory and office blood pressures.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Supported by a project grant (8264) from the GlaxoSmithKline Africa Noncommunicable Disease Open Lab. The trial drugs were donated by Aspen Pharmacare as part of an educational grant.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Mark Huffman of Northwestern University Feinberg School of Medicine for his contributions to the initial version of this manuscript.

We dedicate this work to the late Professor Bongani Mayosi, who championed cardiovascular research in Africa during the past decade and was one of the coprincipal investigators whose contribution made this trial possible.

APPENDIX

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