Hypertension

ORIGINAL ARTICLE

Effect of 3, 2-Drug Combinations of Antihypertensive Therapies on Blood Pressure Variability in Black African Patients: Secondary Analyses of the CREOLE Trial

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BACKGROUND: The effect of 3 commonly recommended combinations of anti-hypertensive agents—amlodipine plus hydrochlorothiazide (calcium channel blocker [CCB]+thiazide), amlodipine plus perindopril (CCB+ACE [angiotensin-converting enzyme]-inhibitor), and perindopril plus hydrochlorothiazide (ACE-inhibitor+thiazide) on blood pressure variability (V) are unknown.

METHODS: We calculated the blood pressure variability (BPV) in 405 patients (130, 146, and 129 randomized to ACE-inhibitor+thiazide, CCB+thiazide, and CCB+ACE-inhibitor, respectively) who underwent ambulatory blood pressure monitoring after 6 months of treatment in the Comparisons of Three Combinations Therapies in Lowering Blood Pressure in Black Africans trial (CREOLE) of Black African patients. BPV was calculated using the SD of 30-minute interval values for 24-hour ambulatory BPs and for confirmation using the coefficient of variation. Linear mixed model regression was used to calculate mean differences in BPV between treatment arms. Within-clinic BPV was also calculated from the mean SD and coefficient of variation of 3 readings at clinic visits.

RESULTS: Baseline distributions of age, sex, and blood pressure parameters were similar across treatment groups. Participants were predominately male (62.2%) with mean age 50.4 years. Those taking CCB+thiazide had significantly reduced ambulatory systolic and diastolic BPV compared with those taking ACE-inhibitor+thiazide. The CCB+thiazide and CCB+ACE-inhibitor groups showed similar BPV. Similar patterns of BPV were apparent among groups using within-clinic blood pressures and when assessed by coefficient of variation.

CONCLUSIONS: Compared with CCB-containing combinations, ACE-inhibitor plus thiazide was associated with higher levels, generally significant, of ambulatory and within-clinic systolic and diastolic BPV. These results supplement the differential ambulatory blood pressure–lowering effects of these therapies in the CREOLE trial. **(*Hypertension*. 2022;79:2593–2600. DOI: 10.1161/HYPERTENSIONAHA.121.18333.)** • **Supplemental Material**

Key Words: blood pressure ■ drug combinations ■ sub-saharan Africa ■ randomized control trial

Even before blood pressure (BP) targets were lowered in more recent hypertension guidelines,[1–3] the majority of patients receiving BP-lowering medications required at least 2 agents to reach the BP targets recommended in most earlier national and international hypertension guidelines.[4–6]

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ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

The impact of 3 commonly recommended combinations of blood pressure–lowering drugs on blood pressure variability has been compared in African patients.

What Is Relevant?

Most patients need at least 2 blood pressure–lowering drugs to reach current blood pressure targets and most guidelines recommend 2 drugs as initial therapy. No randomized trial data are available to inform the optimal combination of drugs to prevent major cardiovascular events in Black patients, but blood pressure variability strongly predicts these events.

Clinical/Pathophysiological implications?

Until randomized trials show which blood pressure–lowering drug combination is the best for African patients, these unique data may help drug selection for Black patients.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
BP	blood pressure
BPV	blood pressure variability
CCB	calcium channel blocker
CREOLE	Comparisons of Three Combinations Therapies in Lowering Blood Pressure in Black Africans trial

Consequently, most current hypertension guidelines[1–3] now recommend that BP-lowering therapy be initiated with 2 agents for most patients. However, robust randomized data informing which combination of agents should be used are limited as reflected by the differences in 2-drug combinations recommended.[1–6] This is particularly true when recommendations are stratified by ethnicity, further reflecting a complete dearth of relevant robust data to inform practice for patients of African, South Asian, or Far Eastern origins.[7]

Nevertheless, almost all guidelines recommend 1 or more of 3 possible combinations—calcium channel blocker (CCB) plus renin angiotensin system-blocker, CCB plus a diuretic or renin angiotensin system-blocker plus a diuretic.

Given evidence of ethnic differences in BP response to different monotherapies,[8,9] and that the majority of patients with hypertension are not white, the need for robust randomized data to inform practice for the majority of the world's patients with hypertension is clear. With this background, the Comparisons of Three Combinations Therapies in Lowering Blood Pressure in Black Africans trial (CREOLE) [10] was carried out in 6 countries in Sub-Saharan Africa comparing the above 3 combinations usually recommended in guidelines. Due to financial constraints, the primary outcome of the CREOLE trial was ambulatory systolic BP, and CREOLE showed that the 2 combinations containing a CCB were superior to the ACE (angiotensin-converting enzyme) inhibitor plus diuretic group from a BP-lowering efficacy viewpoint. The authors of CREOLE concluded that pending further randomized evidence evaluating any differential benefits of the 3 combinations evaluated on major adverse cardiovascular events, the CREOLE data might influence the selection of 2-drug combinations for patients of African origin.[10] Black populations worldwide develop hypertension and associated organ damage at younger ages and have higher rates of hypertension, which is resistant and/or complicated by hypertension-mediated organ damage compared with other ethnic groups. It is therefore critical that optimal management is determined for this population.

In the absence of the necessary differential major adverse cardiovascular event evidence, the CREOLE database allows evaluation of differential impacts of the combinations used on the surrogate outcome of BP variability.

Meanwhile, increasing evidence over the last decade suggest that long-term BP variability often termed visit-to-visit variability observed over several months or years is a better predictor of major adverse cardiovascular event than mean clinic BPs.[11–14] However, these data were preceded in the previous two decades by evidence that shorter term BP variability—within 24 hours—was associated with various types of hypertension-mediated organ damage[15–17] and predicted MACE[18,19] more effectively when compared with mean clinic BPs.[11,20] Given the availability of BP variability in 24-hour ambulatory recordings, taken in the CREOLE trial,[10] the opportunity arose to evaluate whether the differential BP-lowering impacts of the 3 most commonly recommended combinations of antihypertensive medications translated into similarly differential effects on 24-hour BP variability.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The CREOLE trial (10) included 728 male or female Black patients with hypertension from 6 countries in Sub-Saharan Africa. These participants were between 30 and 79 years of age and were recruited if they were either not on treatment

for hypertension and had a mean seated office systolic BP of 150 to 179 mm Hg or if they were receiving monotherapy and had a mean seated office systolic BP of 140 to 159 mm Hg. Other details of trial eligibility criteria have been described previously[10] while pregnant women and those with a history of cardiovascular disease or secondary hypertension were ineligible.

Included patients were randomized to receive 1 of 3 combinations of antihypertensive agents supplied once daily—a CCB, amlodipine 5 mg plus a thiazide diuretic, hydrochlorothiazide 12.5 mg or amlodipine 5 mg plus an ACE-inhibitor, perindopril 4 mg, or perindopril 4 mg plus hydrochlorothiazide 12.5 mg. After 2 months, all drug doses were doubled for a further 4 months. Three seated clinic BPs were recorded at 2, 4, and 6 months of follow-up using the validated semiautomated OMRON M6 Comfort (HEM-7321-E) device and 1 of 3 possible cuff sizes depending on the participants upper arm circumference.

Of the original 728 participants in CREOLE, 621 underwent 24-hour ambulatory BP monitoring at the end of the trial, of whom a subset of 405 patients had 30-minute interval BPs captured during the ambulatory 24-hour period at 6 months available for analyses, to reflect 24-hour ambulatory BP variability.

STATISTICAL ANALYSIS

Baseline characteristics were compared across treatment groups using descriptive statistics for both the subset of 405 patients and the population of 621 patients who underwent ambulatory BP monitoring (ABPM) at 6 months in the original trial. Binary variables were summarized with percentages of the total population of each option, while continuous variables were described by their mean and SD.

ABPM recordings were taken every 30 minutes throughout the 24 hours and were accepted when at least 80% of scheduled measurements (≥38) were recorded and no imputations were performed for missing data.

To estimate the effect of each treatment on BP variability, we used the mean of the SD of the within-participant 24-hour ambulatory systolic and diastolic BP levels, unadjusted for nocturnal BP dipping, as the primary measure of BP variability. Confirmation and consistency of findings was sought by calculating the coefficients of variation of the same ambulatory BP variables. The means of the SDs of all those taking each of the 3 treatment combinations were calculated and compared using a mixed effects regression model, adjusted for site as a random effect, age and baseline ambulatory BP levels. The differences between pairs of treatments at 6 months along with the 95% CIs and *P* are reported in keeping with a pragmatic design whereby baseline blood pressure variability is not required as the basis of comparisons.[21]

ACE-inhibitor plus thiazide was used as the referent group for comparisons with the CCB plus thiazide and CCB plus ACE-inhibitor groups. CCB plus thiazide was used as the referent comparator for comparisons with CCB plus ACE-inhibitor.

Similarly, within-clinic BP variability was evaluated using the mean of the SDs arising from the 2 sets of 3 seated clinic readings taken at each of the 4 and 6-month study follow-up visits. These were compared between each pair of treatments using the methods used for ABPM analyses plus an additional random effect of visit was included. Once again, confirmation of results was investigated by repeating the analysis using the coefficient of variation as the measure of BP variability.

RESULTS

Patient Population

Of the 405 participants who underwent ABPM at baseline and 6 months in the CREOLE trial[10] and who had 30-minute interval ambulatory BPs available, 130, 146, and 129 patients had been randomized to ACE-inhibitor plus thiazide, CCB plus thiazide, and CCB plus ACE-inhibitor, respectively. The average numbers of included BP readings per day at 6 months were 43, 42, and 42 in the 3 groups, respectively.

BASELINE CHARACTERISTICS

The Baseline Characteristics of Patients in the 3 Treatment Groups

The subsample of 405 participants eligible for the BP variability analyses were similar to the 621 subjects who completed ABPM at 0 and 6 months in the CREOLE trial (Table S1). Table 1 shows that these 405 participants were predominately male with mean ages of 51.0±10.3, 49.7±9.7, and 50.3±9.9 years in the CCB plus thiazide, CCB plus ACE-inhibitor, and ACE-inhibitor plus thiazide treatment groups, respectively. Clinic BPs were similar in the 3 treatment groups, but mean baseline ambulatory systolic BP was nonsignificantly higher in the CCB plus ACE-inhibitor group at 148.6 (SD16.1) mm Hg compared with 145.8 (SD 15.1) mm Hg and 145.9 (SD 15.7) mm Hg in the CCB plus thiazide and ACE-inhibitor plus thiazide groups, respectively. Apparent differences in the proportions of patients with diabetes were reported across the 3 groups.

Approximately one-third of participants in each of the 3 groups were taking antihypertensive medication before baseline and a CCB was the most common medication in use.

Effect of Treatment on Mean Blood Pressure Variability

Differences in the mean ambulatory systolic and diastolic BP variability after adjustment for stratification variables and baseline ambulatory systolic and diastolic BP were apparent (Figure 1; Tables S2 and S3). The highest systolic and diastolic BP variability was observed in the ACE-inhibitor plus thiazide group, being significantly higher than that in the CCB plus thiazide

Table 1. Baseline Characteristics of Participants by Randomized Treatment Group

Characteristics	CCB+ thiazide (N=146)	CCB+ACE-inhibitor (N=129)	ACE-inhibitor+ thiazide (N=130)
Mean (SD)			
Age, y	51.0 (10.3)	49.7 (9.7)	50.3 (9.9)
Body mass index, kg/m^2	28.8 (5.7)	28.2 (5.9)	28.0 (6.1)
Clinic BP, mm Hg			
Systolic	159.4 (10.5)	159.4 (11.6)	159.1 (11.4)
Diastolic	98.7 (10.3)	97.7 (11.1)	96.9 (9.8)
ASBP, mm Hg	145.8 (15.1)	148.6 (16.1)	145.9 (15.7)
ADBP, mm Hg	88.5 (10.7)	90.7 (11.4)	87.9 (10.5)
Number, %			
Sex			
Male	92 (63.0)	77 (59.7)	83 (63.9)
Female	54 (37.0)	52 (40.3)	47 (36.2)
Age, y			
≥55	52 (35.6)	40 (31.0)	43 (33.1)
<55	94 (64.4)	89 (69.0)	87 (66.9)
Duration of hypertension <1 y	67 (45.9)	51 (39.5)	53 (40.7)
Diabetes	4 (2.7)	7 (5.4)	14 (10.8)
Dyslipidemia	13 (8.9)	8 (6.2)	8 (6.2)
Current smoking	3 (2.1)	0 (0.0)	1 (0.8)
No previous antihypertensive treatment	99 (67.8)	80 (62.0)	82 (63.1)
Previous antihypertensive treatment			
n (%) on previous treatment	47 (32.2)	49 (38.0)	48 (36.9)
CCBs	27 (57.4)	27 (55.1)	25 (52.1)
Diuretics	13 (27.7)	14 (28.6)	12 (25.0)
ACE inhibitors	3 (6.4)	6 (12.2)	7 (14.6)
ARBs	4 (8.5)	1 (2.0)	3 (6.3)
BBs	0 (0.0)	1 (2.0)	1 (2.1)

CCB, amlodipine; thiazide, hydrochlorothiazide; ACE-inhibitor, perindopril. ACE indicates angiotensin-converting enzyme; ADBP, ambulatory diastolic blood pressure; ARB, angiotensin II receptor blocker; ASBP, ambulatory systolic blood pressure; BB, beta blocker; BP, blood pressure; and CCB, calcium channel blocker.

group (differences in SD=1.18 [95% CI, 2.04–0.33] for systolic BP and 1.19 [95% CI, 2.14–0.23 CI] for diastolic BP [P<0.01 and 0.02]; Figure 1). Similar trends were seen across the 3 treatment groups for differences in the coefficients of variation of mean ambulatory systolic and diastolic BP (Table 2).

Within-clinic systolic and diastolic BP variability as measured by SD (Figure 2) and coefficient of variation (Table 2) were always the highest in the ACE-inhibitor plus thiazide groups. However, while differences in within-clinic BP variability between the ACE-inhibitor plus thiazide and the CCB plus thiazide groups were significant for systolic BP as assessed by SD, the CCB plus ACE-inhibitor group had significantly lower diastolic BP variability than the ACE-inhibitor plus thiazide group (Figure 2; Tables S2 and S3). No significant differences between ambulatory or within-clinic systolic or diastolic BP variability were apparent between the CCB plus thiazide and CCB plus ACE-inhibitor groups, whether measured by SD (Figures 1 and 2) or coefficient of variation (Table 3).

DISCUSSION

There are no definitive randomized data to inform the selection of 2-drug combinations for lowering BP to prevent major cardiovascular events in Black patients with hypertension. Meanwhile, these post hoc analyses of the CREOLE trial[10] comparing the variable impacts of 3 commonly used 2-drug combinations on BP variability provide surrogate data that are supportive of, and commensurate with the main CREOLE results, which showed that a CCB plus either an ACE-inhibitor or a thiazide were superior to an ACE-inhibitor plus a thiazide in terms of lowering ambulatory and clinic BP levels.

Variability in ambulatory systolic and diastolic BP, measured by both SD and coefficient of variation were significantly lower in patients randomized to CCB plus thiazide than to an ACE-inhibitor plus thiazide. No significant differences were apparent between the ambulatory BP variability among those randomized to the CCB plus ACE-inhibitor and the ACE-inhibitor plus thiazide nor between those randomized to a CCB plus a thiazide or an ACE-inhibitor. However, the variability in BP, whether systolic, diastolic, ambulatory or clinic-based, was always the largest among the ACE-inhibitor plus thiazide group, whether measured by SD or coefficient of variation.

Relative to the large numbers of BP measures contributing to the evaluation of variability in the 24-hour ambulatory recordings, the clinic-based variability was only based on 2 sets of 3 BP readings at the 4 and 6-month follow-up visits. Data from the 2-month follow-up visits were excluded from these analyses because the full doses of drugs were not started until the 2-month visit. Consequently, BP levels and therefore variability were different at 2 months and the subsequent visits. Nevertheless, clinic-based systolic BP variability showed similar patterns to those observed in the ambulatory BP data. Hence, in the CREOLE trial, in keeping with previous 24-hour ambulatory BP monitoring studies,[22,23] the more effective agents in terms of BP-lowering were on average more effective in reducing BP variability.

A previous review comparing the impact of antihypertensive drug classes on BP variability showed CCBs to be the most effective agents with nonloop diuretics the next most effective.[14] Furthermore, the impact of CCBs and thiazides on variability when used as monotherapies are maintained when the drugs are used in combination with other drug classes.[24] By contrast, the addition of a

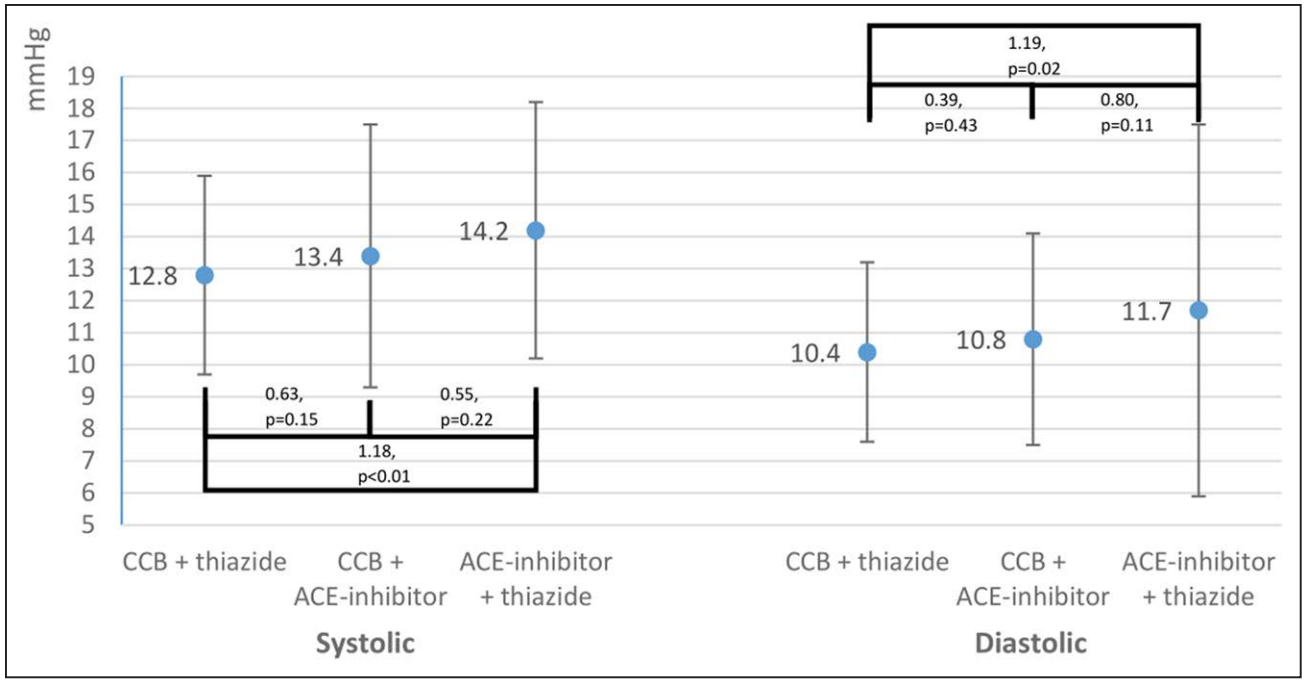

Figure 1. Ambulatory systolic and diastolic blood pressure variability (SD) by treatment group.
Adjusted for site and age strata (less than 55 years/55 years and more) and by baseline ambulatory blood pressure level. ACE-inhibitor indicates perindopril; CCB, amlodipine; SD, standard deviation; and thiazide, hydrochlorothiazide.

renin angiotensin system-blocker to other BP-lowering drug classes reportedly has no impact on BP variability.[24]

Most of these data on BP variability[11–14,24] relate to trials, which predominantly included White patients. Nevertheless, these earlier observations are fully compatible with the findings across the 3 combinations of therapy evaluated in CREOLE.

We evaluated BP variability using both SD and the coefficient of variation, which are both frequently used for this purpose. The use of the former is conceptionally more intuitive while the latter may be considered more robust because, by dividing within patient SD by their mean, a degree of random variation can be overcome.[25]

Table 2. Coefficient of Variation by Treatment Arm for Both SBP and DBP in 24-Hour Ambulatory and Clinical Settings

BP categories evaluated	CCB+thiazide (N=146)	CCB+ACE-inhibitor (N=129)	ACE-inhibitor+ thiazide (N=130)
	Mean (SD)	(Mean (SD)	Mean (SD)
6-mo ASBP CoV	0.099 (0.021)	0.103 (0.031)	0.108 (0.030)
6-mo ADBP CoV	0.133 (0.034)	0.136 (0.040)	0.149 (0.074)
Within-clinic SBP CoV	0.033 (0.017)	0.034 (0.015)	0.038 (0.017)
Within-clinic DBP CoV	0.038 (0.023)	0.036 (0.020)	0.039 (0.022)

CCB, amlodipine; thiazide, hydrochlorothiazide; ACE-inhibitor, perindopril. ACE indicates angiotensin-converting enzyme; ADBP, ambulatory diastolic blood pressure; ASBP, ambulatory systolic blood pressure; CCB, calcium channel blocker; CoV, coefficient of variation; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Importantly, these 2 measures are suitable to measure blood pressure variability in the context that clinic and 24-hour BPs were collected in this trial, whereas variation independent of the mean and the average real variability are less suitable in the context of limited clinic measures. Furthermore, the trends in BP variability across the 3 groups of patients were similar whether measured by SD or coefficient of variation.

While nocturnal BP dipping may impact on 24-hour BP variability,[26] it is reassuring that 78% of CREOLE participants were classified as nondippers[27] and similar low degrees of dipping occurred across all 3 groups of patients. Consequently, we did not apply a weighted SD to adjust for night-time falls.

In 2010, the simultaneous publication of 4 papers greatly increased focus on the potential importance of BP variability and particularly visit-to-visit BP variability.[11–14] These publications apparently influenced the NICE guidelines of 2011[4] to recommend selection of "the best available treatment option to suppress BP variability". However, since then no apparent progress about incorporating robust, valid and yet logistically simple ways of incorporating BP variability into clinical practice has been made.

Meanwhile, better more direct randomized evidence is required to evaluate which combinations of antihypertensive agents are most effective at preventing major cardiovascular events among Black patients with hypertension. Interestingly, the combination of a CCB plus a diuretic is less frequently recommended in guidelines than a CCB plus an ACE-inhibitor or an ACE-inhibitor

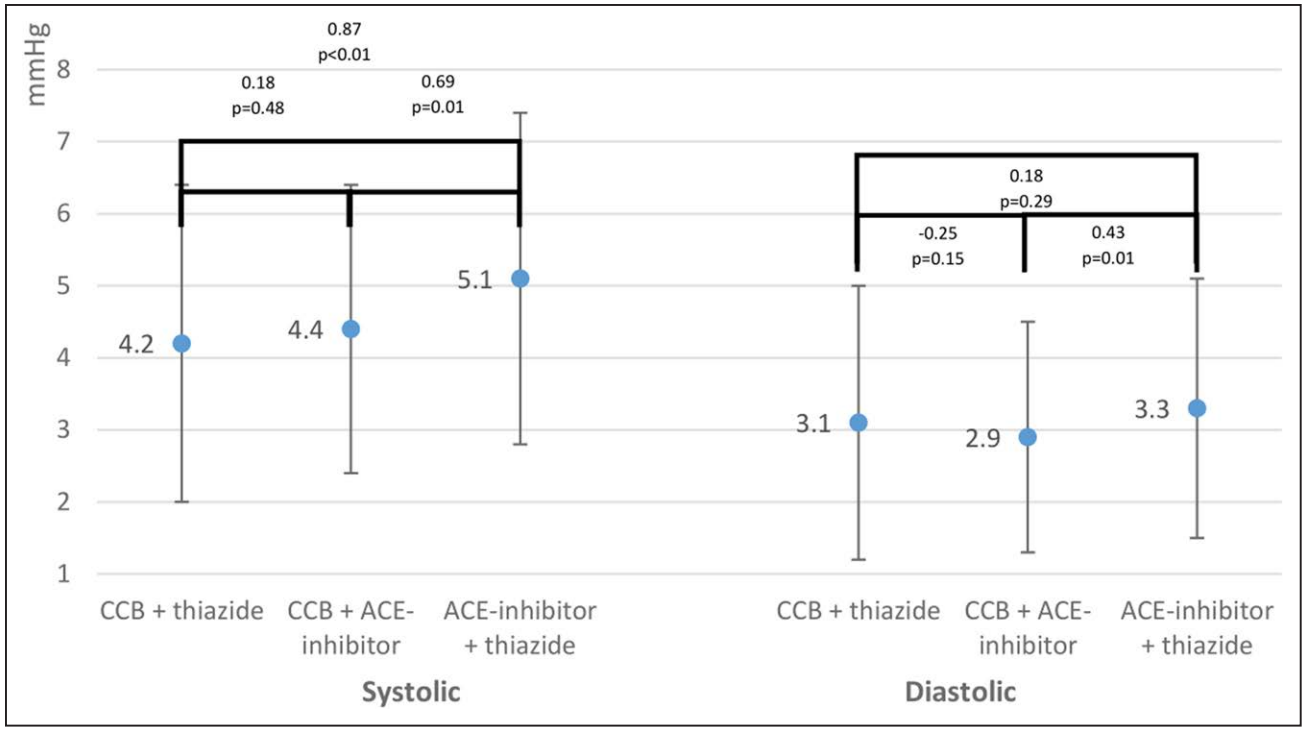

Figure 2. Within-clinic systolic and diastolic blood pressure (BP) variability (SD) by treatment group.
Adjusted for site and age strata (less than 55 years/55 years and more) and baseline clinic BP values. ACE-inhibitor indicates perindopril; CCB, amlodipine; SD, standard deviation; and thiazide, hydrochlorothiazide.

plus a diuretic. This reflects the limited randomized data to recommend the preferential use of CCB plus diuretics, which is effectively limited to the VALUE trial,[28] which was not designed or powered to allow any stratification of results by ethnicity.

The current analyses have several limitations, including the use of 24-hour BP variability rather than longer term variability, which is generally believed to be a better predictor of adverse cardiovascular events.[11] The findings presented here arise from an incomplete sample (405/621) of all those who underwent a 24-hour ABPM at the start and end of the CREOLE trial. However, the sub-sample was apparently very similar to those included in the trial (Table S1). Consequently, it may be reasonable to generalize these findings to the type of Black hypertensive patients from Sub-Saharan Africa included in the trial.

Nevertheless, the findings of these current analyses are unique in providing analyses of 24-hour BP variability in Black patients from Sub-Saharan Africa and in demonstrating clear differences across the 3 pairs of antihypertensive agents evaluated.

In conclusion, pending definitive randomized evidence for the most effective combination(s) of antihypertensive agents to prevent major adverse cardiovascular event in Black patients with hypertension, because BP variability

Table 3. Comparison of CoV Between Treatment Arms for Both SBP and DBP in 24-Hour Ambulatory and Clinic Settings

BP categories evaluated	CCB+thiazide vs ACE-inhibitor+thiazide (95% CI) *P* value	CCB+ACE-inhibitor vs ACE-inhibitor+thiazide (95% CI) *P* value	CCB+thiazide vs CCB+ACE-inhibitor (95% CI) *P* value
Difference in CoV 6-mo 24 h ambulatory systolic BP (N=405)	−0.007 (−0.013 to −0.001)	−0.003 (−0.010 to 0.003)	−0.004 (−0.010 to 0.002)
	0.026	0.355	0.202
Difference in CoV 6-mo 24-h ambulatory diastolic BP (N=405)	−0.015 (−0.029 to −0.002)	−0.012 (−0.026 to 0.001)	−0.003 (−0.016 to 0.010)
	0.023	0.080	0.641
Difference in CoV within-clinic systolic BP (N=405)	−0.005 (−0.009 to −0.001)	−0.004 (−0.008 to 0.000)	0.001 (−0.005 to 0.002)
	0.009	0.061	0.484
Difference in CoV within-clinic diastolic BP (N=405)	−0.001 (−0.007 to 0.004)	−0.003 (−0.008 to 0.002)	0.002 (−0.003 to 0.007)
	0.564	0.213	0.481

CCB, amlodipine; thiazide, hydrochlorothiazide; ACE-inhibitor, perindopril. ACE indicates angiotensin-converting enzyme; BP, blood pressure; CCB, calcium channel blocker; CoV, coefficient of variation; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

does seem to be a surrogate for major cardiovascular outcomes, the current findings may help, along with the previous CREOLE trial findings[10] to inform the selection of BP-lowering medications for Black patients.

PERSPECTIVES

Combination therapy is recommended in many current guidelines as initial therapy for most patients with hypertension. However, data are not available to inform the best treatment combinations to produce optimal cardiovascular protection in hypertensive patients of African origin. Pending generation of such data, evidence of differences in surrogate markers of cardiovascular protection associated with BP control may help to inform optimal treatment. These data based on the CREOLE trial show clear differences in the impact of 3 commonly used treatment combinations on BP variability.

Given the established and clear associations between BP variability and adverse cardiovascular events, these data maybe useful to help resolve hitherto unclear treatment decisions regarding the management of hypertension in patients of African origin.

ARTICE INFORMATION

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Disclosures

B. Rayner has participated on a Data Safety Monitoring Board or Advisory Group on the Original CREOLE trial and also on the Hypertension in Africa Study (Servier). E. Jones has received payments to her institution for part of the funding of the original CREOLE research project. N. Poulter has received financial support from several pharmaceutical companies which manufacture BP-lowering agents, for consultancy fees (Servier), research projects and staff (Servier, Pfizer) and for arranging and speaking at educational meetings (AstraZeneca, Lri Therapharma, Napi, Servier, Sanofi, Eva Pharma, Pfizer, Alkem Laboratories and Glenmark Pharma). He holds no stocks and shares in any such companies. He is the Chairman of the Steering Committee of the TIME trial.

REFERENCES

1. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension*. 2018;71:1269–1324. doi: 10.1161/HYP.0000000000000066
2. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018;36:1953–2041. doi: 10.1097/HJH.0000000000001940.
3. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, et al. 2020 International society of hypertension global hypertension practice guidelines. *Hypertension*. 2020; 75:1334–1357. doi: 10.1161/HYPERTENSIONAHA.120.15026
4. National Institute for Health and Clinical Excellence, Hypertension (CG127): 2011 clinical management of primary hypertension in adults. Accessed September 2, 2022. https://www.nice.org.uk/guidance/cg127
5. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, Flack JM, Carter BL, Materson BJ, Ram CV, et al. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of hypertension and the international society of hypertension. *J Clin Hypertens*. 2014;16: 14–26. doi: 10.1111/jch.12237
6. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–219. doi: 10.1093/eurheartj/eht151
7. Park IU, Taylor AL. Race and ethnicity in trials of antihypertensive therapy to prevent cardiovascular outcomes: a systematic review. *Ann Fam Medm*.2007;5:444–452. doi: 10.1370/afm.708
8. Cushman WC, Ford CE, Cutler JA Margolis KL, Davis BR, Grimm RH, Black HR, Hamilton BP, Holland J, Nwachuku C, et al. ALLHAT collaborative research group. success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens (Greenwich)*. 2002;4:393–404. doi: 10.1111/j.1524-6175.2002.02045.x.
9. Gupta AK, Poulter NR, Dobson J, Eldridge S, Cappuccio FP, Caulfield M, Collier D, Cruickshank JK, Sever PS, Feder G. Ethnic differences in blood pressure response to first and second-line antihypertensive therapies in patients randomized in the ASCOT Trial. *AM J Hypertens*. 2010. 23:1023–1030. doi: 10.1038/ajh.2010.105.
10. Ojji DB, Mayosi B, Francis V, Badri M, Cornelius V, Smythe W, Kramer N, Barasa F, Damasceno A, Dzudie A, et al; CREOLE Study Investigators. Comparison of dual therapies for lowering blood pressure in black africans. *N Engl J Med*. 2019;380:2429–2439. doi: 10.1056/NEJMoa1901113
11. Rothwell PM, Howard SC, Dolan E, Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lance*. 2010; 375:895–905. doi: 10.1016/S0140-6736(10)60308-X.
12. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*. 2010;375:938–948. doi: 10.1016/S0140-6736(10)60309-1
13. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS; ASCOT-BPLA and MRC Trial Investigators. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol*. 2010; 9:469–480.
14. Webb AJS, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet*. 2010;375:906–915. doi: 10.1016/S0140-6736(10)60235-8

15. Mancia G, Parati G, Hennig M, Flatau B, Omboni S, Glavina F, Costa B, Scherz R, Bond G, Zanchetti A; ELSA Investigators. Relation between blood pressure variability and carotid artery damage in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis (ELSA). *J Hypertens*. 2001;19:1981–1989. doi: 10.1097/00004872-200111000-00008
16. Shintani Y, Kikuya M, Hara A, Ohkubo T, Metoki H, Asayama K, Inoue R, Obara T, Aono Y, Hashimoto T,et al. Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: the ohasama study. *J Hypertens*. 2007; 25:1704–1710. doi: 10.1097/HJH.0b013e328172dc2e.
17. Madden JM, O'Flynn AM, Fitzgerald AP, Kearney PM. Correlation between short-term blood pressure variability and left-ventricular mass index: a meta-analysis. *Hypertens Res*. 2016;39:171–177. doi: 10.1038/hr.2015.126
18. Kikuya M, Hozawa A, Ohokubo T, Tsuji I, Michimata M, Matsubara M, Ota M, Nagai K, Araki T, Satoh H, et al. Prognostic significance of blood pressure and heart rate variabilities: the ohasama study. *Hypertension*. 2000;36:901–906. doi: 10.1161/01.hyp.36.5.901
19. Hansen TW Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, Richart T, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, et al. International database on ambulatory blood pressure in relation to cardiovascular outcomes investigators. International database on ambulatory blood pressure in relation to cardiovascular outcomes investigators. Prognostic value of reading-to-reading blood pressure variability over 24 h in 8938 subjects from 11 populations. *Hypertension*. 2010;55:1049–1057. doi: 10.1161/HYPERTENSIONAHA.109.140798
20. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, McManus RJ. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2016;354:i4098. doi: 10.1136/bmj.i4098
21. Vickers AJ, Altman DG. Statistics notes: analysing controlled trials with baseline and follow up measurements. *BMJ*. 2001;323:1123–1124. doi: 10.1136/bmj.323.7321.1123
22. Mancia G, Omboni S, Parati G, Ravogli A, Villani A, Zanchetti A. Lack of placebo effect on ambulatory blood pressure. *Am J Hypertens*. 1995;8:311–315. doi: 10.1016/0895-7061(94)00250-F
23. Parati G, Ochoa JE, Lombardi C, Bilo G. Blood pressure variability: assessment, predictive value, and potential as a therapeutic target. *Curr Hypertens Rep*. 2015;17:537. doi: 10.1007/s11906-015-0537-1
24. Levi-Marpillat N, Macquin-Mavier I, Tropeano AI, Parati G, Maison P. Antihypertensive drug classes have different effects on short-term blood pressure variability in essential hypertension. *Hypertens Res*. 2014;37:585–590. doi: 10.1038/hr.2014.33
25. Del Giorno R, Balestra L, Heiniger PS, Gabutti L. Blood pressure variability with different measurement methods: reliability and predictors. A proof of concept cross sectional study in elderly hypertensive hospitalized patients. *Medicine (Baltimore)*. 2019;98:e16347. doi: 10.1097/MD.0000000000016347
26. Bilo G, Giglio A, Styczkiewicz K, Caldara G, Maronati A, Kawecka-Jaszcz K, Mancia G, Parati G. A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J Hypertens*. 2007;25:2058–2066. doi: 10.1097/HJH.0b013e32829c6a60
27. Ingabire PM, Ojji DB, Rayner B, Ogola E, Damasceno A, Jones E, Dzudie A, Ogah OS, Poulter N, Sani MU, et al; CREOLE Study Investigators. High prevalence of non-dipping patterns among Black Africans with uncontrolled hypertension: a secondary analysis of the CREOLE trial. *BMC Cardiovasc Disord*. 2021;21:254. doi: 10.1186/s12872-021-02074-7
28. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, et al. VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031. doi: 10.1016/S0140-6736(04)16451-9