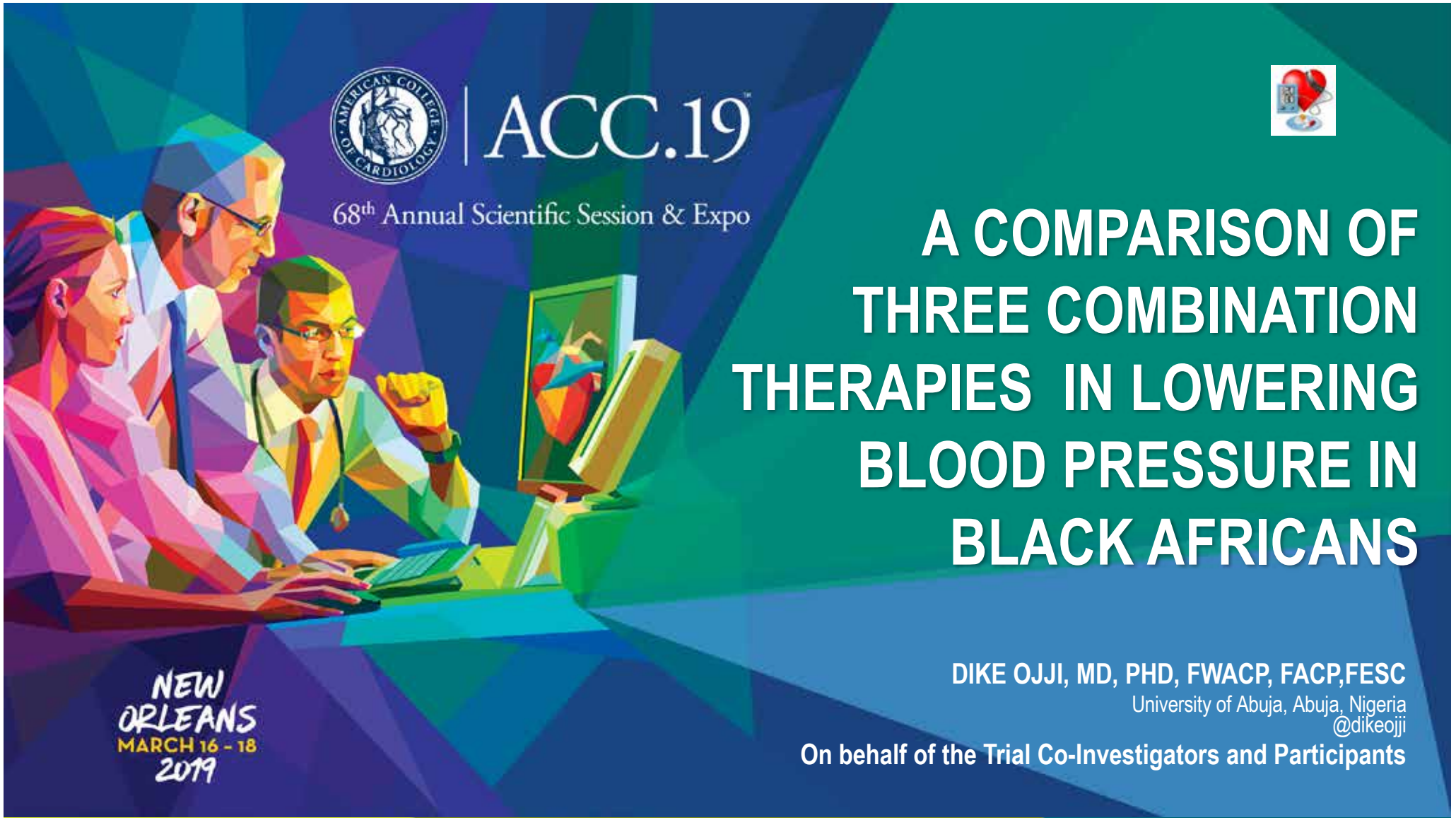

A COMPARISON OF THREE COMBINATION THERAPIES IN LOWERING BLOOD PRESSURE IN BLACK AFRICANS

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On behalf of the Trial Co-Investigators and Participants

Rationale

- Although there are many possible anti-hypertensive combination therapies, the best combination for the black African population has not been identified and guideline recommendations are inconsistent.
- There is a high burden of hypertension and its complications in this population.
- Most patients with hypertension require ≥2 antihypertensive agents to reach current BP targets.
- Hitherto no RCTs have compared the efficacy of contemporary 2-drug combination therapies in this population.

Hypothesis

Therapy with a combination of Amlodipine + HCTZ will be more efficacious than the combinations of Amlodipine+Perindopril and Perindopril + HCTZ in lowering mean 24 hour ambulatory systolic blood pressure (ASBP) levels.

Primary Objective

To compare the efficacy of three "free" combinations of two-drug anti-hypertensive agents:

Amlodipine + Hydrochlorothiazide

Amlodipine + Perindopril

Perindopril + Hydrochlorothiazide

on mean 24 hour ASBP in black African hypertensive patients.

Key Inclusion Criteria

- Male or female patients aged 30-79 years of age with:
- Sitting office SBP ≥140 mmHg and < 160 mmHg on one antihypertensive agent
- Or sitting office SBP ≥ 150 mmHg and < 180 mmHg on no antihypertensive treatment.

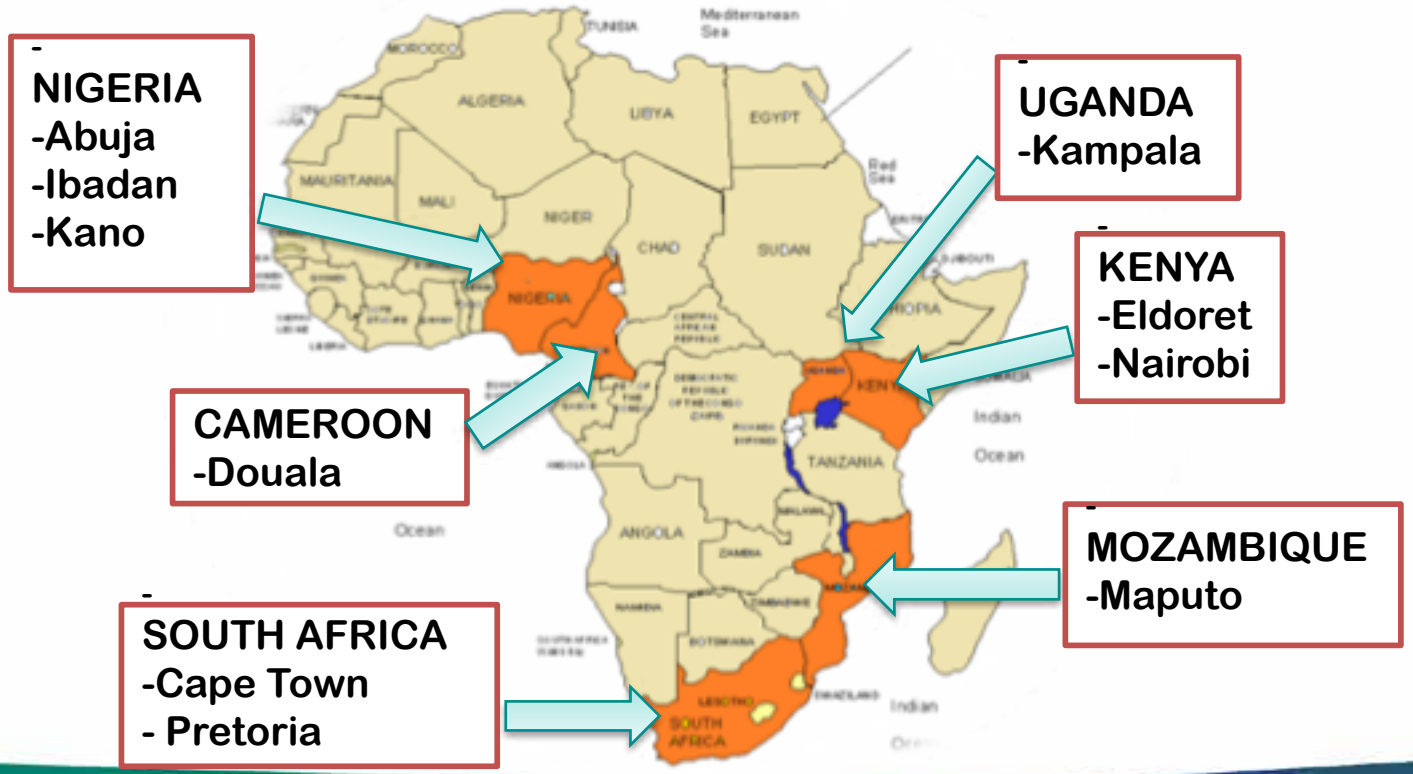
Key Exclusion Criteria

- Those with a history of CHD, stroke or CKD
- Those with a history of intolerance to any of the study medication
- Patients with known or suspected secondary hypertension
- Any other concomitant illness, physical or mental impairment that could interfere with effective conduct of the study
- Pregnant women

Trial Design Features

- Randomised single-blind, parallel group, 3-arm superiority trial.
- Location: 6 Sub-Saharan Countries : 10 sites
- Sample size: Minimum of 702: power (84%) to detect the clinically meaningful difference in mean 24 Hr ASBP of 3.0mmHg assuming SD of 9mmHg with 10% drop out rate.
- Visit schedule: Baseline, 2, 4 and 6 months
- Office BP methods: Baseline, 2, 4 and 6 months (3X with mean of last 2) using semi-automated device (Omron M6 HEM 7321-E)
- ABPM methods: Baseline and 6months (every 30 minutes for 24 hours using Meditech monitors (ABPM- 05 model)

Study sites and Trial Design Features



Medications

- **Amlodipine + Perindopril**

  5/4mg (0-2 months); 10/8mg (2-6 months)

- **Amlodipine + HCT**

  5/12.5mg (0-2 months);10+25 mg (2-6 months)

- **Perindopril + HCT**

  4/12.5mg (0-2 months); 8+25 mg (2-6 months)

Primary Endpoint

- **Change in ASBP from baseline to 6 months**

Secondary Endpoints

Change in the following from baseline to 6 months:

- 24 hour ADBP
- Daytime and night time ABP levels
- Office systolic and diastolic BP
- Blood Analytes (lipids, glucose, renal function)
- BP control rates (office BP < 140/90 mmHg) at 2, 4 & 6 months
- Response rates (office BP reduction > 20mmHg SBP and >10 mmHg DBP) at 2, 4 & 6 months
- Adverse event rate

Baseline Demographic and Clinical Characteristics by Treatment Group (621 patients)

Characteristic	Amlodipine-Hydrochlorothiazide Group (n= 216)	Amlodipine-Perindopril Group(n=205)	Perindopril-Hydrochlorothiazide Group (n=200)
Female no (%)	136 (63.0)	128 (62.4)	129 (64.5)
Age, Mean (SD), years	51.2 (10.9)	50.9 (10.8)	50.9 (10.2)
<55 year no (%)	132 (61.1)	131 (63.9)	128 (64.0)
Body Mass Index, Mean (SD)-kg/m^2	28.7 (5.5)	28.5 (5.7)	27.8 (6.1)
Clinic Systolic BP, Mean (SD)-mmHg	158.0 (11.0)	158.0 (11.1)	158.3 (13.0)
Clinic Diastolic BP, Mean (SD)-mmHg	98.3 (10.4)	97.3 (10.6)	97.2 (10.0)
ASBP, Mean (SD)-mmHg	145.6 (14.6)	147.6 (16.5)	146.0 (15.7)
ADBP, Mean (SD)-mmHg	88.3 (10.5)	90.0 (11.9)	88.3 (10.4)
Pulse, Mean (SD)-beats/minute	83.3 (13.8)	80.1(13.7)	81.8 (14.0)
Current BP-lowering agent- no. (%)			
Nil	150(69.4)	132(64.4)	133(66.5)
CCB	34(15.7)	39(19.0)	34(17.0)
Diuretics	22(10.2)	22(10.7)	18(9.0)
ACEIs	5(2.3)	9(4.4)	8(4.0)
ARBS	4(1.9)	2 (1.0)	6(3.0)
BB	1(0.5)	1(0.5)	1(0.5)

Adjusted Mean Differences in ABP Reduction between Treatment Groups

Variable	Aml + HCTZ vs Per + HCTZ		Aml + HCTZ v Aml+ Per		Aml +Per vs Per + HCTZ	
	Mean Difference (95% CI)	p	Mean Difference (95% CI)	p	Mean Difference (95% CI)	p
24 Hour ASBP	-3.14 (-5.90, -0.38)	0.03	-0.14 (-2.90, 2.61)	0.92	-3.00 (-5.81, -0.20)	0.04
24 Hour ADBP	-1.05 (-2.67, 0.55)	0.20	-0.41 (-2.01,1.18)	0.61	-0.64 (-2.27, 0.98)	0.44
Day(12Hr) ASBP	-1.93 (-4.75, 0.89)	0.18	0.63 (-2.17, 3.44)	0.66	-2.56 (-5.42, 0.30)	0.08
Night-time ASBP	-3.79 (-6.80, -0.78)	0.01	-0.41 (-3.38, 2.56)	0.79	-3.38 (-6.43, -0.33)	0.03
Day (12 Hr) ADBP	-0.76 (-2.50, 0.98)	0.93	-0.21 (-1.95, 1.52)	0.81	-0.55 (-2.31, 1.21)	0.54
Night-time ADBP	-1.52 (-3.22, 0.17)	0.08	-0.69 (-2.36, 0.98)	0.42	-0.83 (-2.55, 0.89)	0.35

Model I: Adjusted For randomization stratification variables (Age (< 55/>55) and site, and baseline ASBP

Adjusted Mean Differences in ABP Reduction between Treatment Groups

Variable	Aml + HCTZ vs Per + HCTZ		Aml + HCTZ v Aml+ Per		Aml +Per vs Per + HCTZ	
	Mean Difference (95% CI)	p	Mean Difference (95% CI)	p	Mean Difference (95% CI)	p
24 Hour ASBP	-3.57 (-6.31, -0.83)	0.01	-0.37 (-3.09, 2.35)	0.79	-3.20 (-5.95, -0.46)	0.02
24 Hour ADBP	-1.37 (-2.97, 0.23)	0.09	-0.63 (-2.22, 0.96)	0.44	-0.74 (-2.34, 0.86)	0.36
Day(12Hr) ASBP	-2.52 (-5.30, 0.24)	0.07	0.24 (-2.52, 3.00)	0.87	-2.77 (-5.55, 0.01)	0.05
Night-time ASBP	-4.31 (-7.28, -1.33)	0.005	-0.64 (-3.56, 2.28)	0.67	-3.67 (-6.64, -0.69)	0.02
Day (12 Hr) ADBP	-1.13 (-2.87, 0.61)	0.20	0.49 (-2.23, 1.24)	0.58	-0.64 (-2.38, 1.11)	0.47
Night-time ADBP	-1.86 (-3.56, -0.16)	0.03	-0.89(-2.56, 0.78)	0.30	-0.96 (-2.67, 0.73)	0.27

Model II: sensitivity analysis: Adjusted for randomization stratification variables (age (< 55/≥55) and site, baseline ASBP, diabetes mellitus, gender, dyslipidaemia, BMI, heart rate and duration of hypertension

Adjusted Mean Differences in Clinic BP Reduction between Treatment Groups

Variable	Aml+ HCTZ versus Per + HCTZ	Aml + HCTZ versus Aml + Per	Aml + Per versus Per + HCTZ
	Mean Difference (95% CI)	Mean Difference (95% CI)	Mean Difference (95% CI)
2 Month Office SBP	-5.72 (-9.14, -2.30)	-5.14 (-8.3, -1.74)	-0.58 (-3.84, 2.65)
4 Month Office SBP	-4.76 (-7.88, -1.63)	-0.04 (-3.14, 3.07)	-4.72 (-7.88, -1.56)
6 Month Office SBP	-7.15 (-10.25, -4.06)	-1.61(-4.69, 1.47)	-5.55 (-8.69, -2.41)
2 Month Office DBP	-3.49 (-5.49, -1.49)	-2.81(-4.79, -0.82)	-0.68 (-2.71, -1.34)
4 Month Office DBP	-2.39 (-4.24, -0.53)	-0.14 (-1.70, 1.98)	-2.53 (-4.23, -0.53)
6 Month Office DBP	-4.86 (-6.84, -2.89)	-1.27 (-3.23, 0.70)	-3.60 (-5.60, -1.60)

Comparison of BP Control and Response Rates between Treatment Groups

Variable	Aml+ HCTZ versus Per + HCTZ			Aml +HCTZ versus Aml + Per			Aml + Per versus Per + HCTZ		
	Aml+ HCTZ (n=216) (%)	Per + HCTZ (n=200) (%)	Difference (95%CI)	Aml+ HCTZ (n=216) (%)	Aml + Per (n=216) (%)	Difference (95%CI)	Aml + Per (n=200) (%)	Per+ HCTZ (n=205) (%)	Difference (95%CI)
6 months response rate	81.9	70.1	11.8 (3.60,19.8)	80.1	81.9	1.8 (-5.69,9.34)	70.1	80.1	10.0 (1.58,18.27)
6 months control rate	75.9	60.0	15.9 (6.94,24.5)	73.7	75.9	2.2 (-6.07,10.4)	60.0	73.7	13.7 (4.53,22.57)

Adherence and Incidence of Adverse Events in Safety Population (728 Patients) by Treatment Group

	Aml +HCTZ (244)	Aml + Per (243)	Per + HCTZ (241)	Total (728)
Adherence, Mean (SD)	80.6 (32.5)	79.8 (33.9)	79.5 (32.8)	80.0 (33.0)
Adverse Events				
Dry Cough- n (%)	0 (0.0)	14 (5.8)	12 (5.0)	26 (3.6)
Pedal Swelling- n (%)	10 (4.1)	9 (3.7)	1 (0.4)	20 (2.7)
Palpitations- n (%)	5 (2.0)	7 (2.9)	1 (0.4)	13 (1.8)
Headaches- n (%)	5 (2.0)	4 (1.6)	2 (0.8)	11 (1.5)
Angioedema- n (%)	0 (0.0)	2(0.8)	3 (1.2)	5 (0.7)
Dizziness- n (%)	4 (1.6)	1(0.4)	4 (1.7)	9 (1.2)
Hypokalemia*- n (%)	13 (5.3)	1 (0.4)	4 (1.7)	18 (2.5)
Death- n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Others- n (%)	2 (0.81)	1 (0.4)	1 (0.4)	4 (0.6)
Total-n (%)	39 (16.0)	39 (16.0)	28 (11.6)	106 (14.6)

Others = Erectile Dysfunction, Fainting, Frequent urination

***K<3.2mmol/L**

Study Summary

- Patients who received Amlodipine plus HCTZ and Amlodipine plus Perindopril had a greater reduction in ASBP compared to those who received Perindopril plus HCTZ.
- Similar findings applied to night-time ASBP, office BP, BP control and BP response.
- Dry cough and angioedema were seen in 5.4% and 1.0 % respectively of patients that received perindopril.
- And pedal oedema in 3.9% of those that received Amlodipine, and hypokalemia in 5.3% of the patients who received Amlodipine and HCTZ.

Clinical Implications

- Given that Amlodipine plus HCTZ and Amlodipine plus Perindopril had similar effects on BPs, drug choice may be further influenced by side effect considerations – particularly cough and angioedema vs hypokalaemia.
- Pending trial evidence comparing the effects of these combinations on cardiovascular outcomes, these unique data may be useful to influence antihypertensive drug selection for black patients, at least those from SSA.

Acknowledgement

- Funded by GSK Non-Communicable Disease Open Lab Grant for sub Saharan Africa.

- The investigational medicinal products were donated by Aspen Pharmacare as part of their educational grant.

- CO- PIS (Prof Neil Poulter and Late Prof Bongani Mayosi); site PIS and all other investigators.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Dual Therapies for Lowering Blood Pressure in Black Africans

D.B. Ojji, B. Mayosi,* V. Francis, M. Badri, V. Cornelius, W. Smythe, N. Kramer, F. Barasa, A. Damasceno, A. Dzudie, E. Jones, C. Mondo, O. Ogah, E. Ogola, M.U. Sani, G.L. Shedul, G. Shedul, B. Rayner, I.G. Okpechi, K. Sliwa, and N. Poulter, for the CREOLE Study Investigators†

THANK YOU VERY MUCH