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Adeseye Akintunde
Ladoke Akintola University of Technology

Justus Nondi
Egerton University

Kennedy Gogo
Egerton University

Erika S.W. Jones
Groote Schuur Hospital

Brian L. Rayner
Groote Schuur Hospital

See next page for additional authors

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Adeseye Akintunde,[1] Justus Nondi,[2] Kennedy Gogo,[2] Erika S. W. Jones,[3] Brian L. Rayner,[3] Daniel G. Hackam,[4,5] and J. David Spence[5]

OBJECTIVES
African and African American hypertensives tend to retain salt and water, with lower levels of plasma renin and more resistant hypertension. We tested the hypothesis that physiological phenotyping with plasma renin and aldosterone would improve blood pressure control in uncontrolled hypertensives in Africa.

METHODS
Patients at hypertension clinics in Nigeria, Kenya, and South Africa with a systolic blood pressure >140 mm Hg or diastolic pressure > 90 mm Hg despite treatment were allocated to usual care (UC) vs. physiologically individualized care (PhysRx). Plasma renin activity and aldosterone were measured using ELISA kits. Patients were followed for 1 year; the primary outcome was the percentage of patients achieving blood pressure <140 mm Hg and diastolic <90 mm Hg.

RESULTS
Results are presented for the 94/105 participants who completed the study (42 UC, 52 PhysRx). Control of both systolic and diastolic pressures was obtained in 11.1% of UC vs. 50.0% of PhysRx ($P = 0.0001$). Systolic control was achieved in 13.9% of UC vs. 60.3% of PhysRx ($P = 0.0001$); diastolic control in 36.1% of UC vs. 67.2% of PhysRx, vs. ($P = 0.003$). Number of visits and total number of medications were not significantly different between treatment groups, but there were differences across the sites. There were important differences in prescription of amiloride as specified in the PhysRx algorithm.

CONCLUSIONS
Physiologically individualized therapy based on renin/aldosterone phenotyping significantly improved blood pressure control in a sample of African patients with uncontrolled hypertension. This approach should be tested in African American and other patients with resistant hypertension. Registered as ISRCTN69440037

Keywords: African; aldosterone; Black; blood pressure; hypertension; personalized medicine; renin; resistant hypertension; race.

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Laragh first proposed[1] that management of hypertension could be improved by measuring plasma renin activity (PRA). In 1999 Spence reported[2] on 20 years' experience of using stimulated PRA to manage resistant hypertension in >4,000 patients. Identifying the cause of the hypertension was the key to obtaining control in patients with severe resistant hypertension, and primary aldosteronism due to bilateral adrenocortical hyperplasia was more common in black patients. At that time an aldosterone assay was not available to the clinic, so Liddle syndrome was not diagnosed. Reasons why this approach was not widely adopted may include that it is not helpful in patients whose blood pressure is easily controlled, and failure to measure stimulated PRA. Unstimulated PRA is usually low because of salt intake; stimulation spreads out the range of PRA so that low and suppressed levels can be appreciated.[3]

Black patients tend to retain salt and water and have suppressed levels of plasma renin.[4] There are some race-based guidelines for treatment of hypertension in the United States[5]; Bonham *et al.*[6] suggested it may be possible to move beyond race with "precision medicine". However, there are many variants of at least 10 genes that would increase salt and water retention (online Supplementary eTable 1),[7] and specific treatments have not yet been defined for each of these conditions. Therefore, in a polygenic condition such as hypertension, individualized therapy based on physiological phenotyping[8] might confer advantages, including lower cost, and the ability to select therapy not yet directed by genotyping.

In Africans and African Americans, there may be a selective advantage to salt and water retention in hot arid climates,[9] in survival of the Atlantic crossing between decks of slave ships transporting African slaves to America, and survival of the first few years in slavery.[10,11]

Correspondence: J. David Spence (dspence@robarts.ca).

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[1]Ladoke Akintola University of Technology Teaching Hospital, Ogbomoso, Oyo State, Nigeria; [2]Department of Medicine, Egerton University, Nakuru, Kenya; [3]Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; [4]Departments of Medicine and Biostatistics and Epidemiology, Western University, London, ON, Canada; [5]Department of Neurology and Clinical Pharmacology, Stroke Prevention and Atherosclerosis Research Centre, Robarts Research Institute, Western University, London, ON, Canada.

A randomized trial of this approach by Egan *et al.*,[12] in 77 patients randomized to usual care (UC) vs. renin-based therapy, reported lower systolic pressures, a trend to improved blood pressure control, and a greater reduction of medication needed among patients with volume hypertension (i.e., low renin hypertension) using PRA to guide therapy.

Measuring plasma renin alone is helpful, but there are two main phenotypes among patients with suppressed levels of plasma renin: low renin/high aldosterone, implying primary aldosteronism (PA) (often due to bilateral adrenocortical hyperplasia),[13] and a low renin/low aldosterone phenotype, implying a variant of the renal epithelial sodium channel and/or other variants affecting renal tubular absorption of sodium and water that suppress both plasma renin and aldosterone. It is therefore important to distinguish these phenotypes[14]: patients with PA would best be treated with aldosterone antagonists such as spironolactone or eplerenone,[15] whereas the specific treatment for Liddle syndrome is amiloride,[16] an epithelial sodium channel blocker. Amiloride may also be useful in patients with other causes of the Liddle phenotype (low renin/low aldosterone), and is also useful in patients with primary aldosteronism (particularly those who cannot tolerate adequate doses of spironolactone because of gynecomastia, or cannot afford to pay for eplerenone).

Black patients have salt and water retention,[17] are more likely to have low levels of plasma renin, and are more sensitive to aldosterone.[18] This may explain why in the United States, Black patients, who have twice the risk of stroke, are less likely to have their blood pressure controlled (61.7% vs. 70.1% for Whites), despite greater awareness of their hypertension, greater likelihood of being treated, and greater likelihood of being treated more intensively.[19]

Hemorrhagic stroke, which is almost entirely preventable by controlling blood pressure,[20] is disproportionately common in sub-Saharan Africa[21] and in African Americans.[22]

In this study, we tested the hypothesis that treatment based on physiological phenotyping, using PRA and aldosterone to select appropriate therapy, may improve blood pressure control compared to usual therapy, in patients with uncontrolled hypertension attending hypertension clinics in Africa.

METHODS

Patients attending hypertension clinics in Nigeria, Kenya, and South Africa were enrolled in the study. Uncontrolled hypertension was defined as a systolic blood pressure >140 or diastolic blood pressure >90 despite usual treatment at each clinic. UC was nominally based on guidelines in place at each site: at the Nigerian site the guidelines of the International Society of Hypertension and the World Health Organization; at the South African site, the South African hypertension guidelines; at the Kenyan site, the Joint National Committee (JNC) 8 guideline. The participants were allocated to UC, vs. therapy guided by their physiological phenotype, based on plasma renin and aldosterone (PhysRx). The algorithm for adjusting therapy based on plasma renin and aldosterone is shown in Table 1.

PRA and plasma aldosterone were sampled at the time of their randomization while taking their usual medications (all of which included drugs that stimulate PRA), while seated. Levels were measured using kits from Diagnostics Biochem Inc. (London, Canada). Blood samples were not placed on ice; they were taken immediately to the biochemistry laboratory. The PRA ELISA kit determined the concentration of Angiotensin I in EDTA-Plasma using a very specific anti-Angiotensin I antibody, a biotinylated Angiotensin I tracer and other reagents. PRA was then calculated from the difference in concentration of Angiotensin I in samples that were incubated either at 4 °C or 37 °C at slightly acidic pH for approximately 2 hours. The 95% reference range for normal salt intake is 0.015–12.2 ng/ml.h. Aldosterone concentration was determined directly in the same samples from the DBC ELISA, which also relies on a highly specific anti-aldosterone antibody. The 95% confidence range for upright sampling

Table 1. Physiologically individualized therapy[a] based on renin/aldosterone profile

	Primary hyperaldosteronism	Liddle's syndrome and variants (mutations affecting renal Na^+ channel)	Renal/renovascular
Renin	Low[b]	Low	High
Aldosterone	High[b]	Low	High
Primary treatment	Aldosterone antagonist (spironolactone or eplerenone)	Amiloride	Angiotensin receptor blocker[c]
	Amiloride for men where eplerenone is not available (rarely surgery)		(rarely revascularization)

Abbreviation: ACE, angiotensin-converting enzyme.

[a]It should be stressed that this approach is suitable for tailoring medical therapy in resistant hypertensives; further investigation would be required to justify adrenalectomy or renal revascularization.

[b]Levels of plasma renin and aldosterone must be interpreted in the light of the medication the patient is taking at the time of sampling. In a patient taking an angiotensin receptor blocker (which would elevate renin and lower aldosterone), a plasma renin that is in the low normal range for that laboratory, with a plasma aldosterone in the high normal range, probably represents primary hyperaldosteronism, for the purposes of adjusting medical therapy.

[c]Angiotensin receptor antagonists are less effective because of aldosterone escape *via* non-ACE pathways such as chymase and cathepsin; renin inhibitors are seldom used.

(Reproduced by permission of Elsevier from Spence JD. Lessons from Africa: the importance of measuring plasma renin and aldosterone in resistant hypertension. *Can J Cardiol* 2012; 28:254–257.)

with a normal salt intake is 0–199 pG/ml. Both kits present good precision with coefficients of variation intra- and inter-assay smaller than 9% (PRA kit) and 13% (aldosterone kit).

Blood pressure was measured seated, in the arm in which systolic pressure was higher at the first visit, using automated blood pressure devices, taking the mean of 3 readings after discarding the first. Blood pressure was measured at the Nigerian site using an Accusson mercury sphygmomanometer; at the South African site with a Spacelabs device programmed to measure blood pressure every minute; at the Kenyan site with an Omron automated device.

The primary outcome was blood pressure control after 1 year, defined as a systolic blood pressure <140 mm Hg, and a diastolic blood pressure <90 mm Hg. Other variables recorded included baseline sodium/creatinine ratio, medications at baseline and end of study, and number of visits. Estimated glomerular filtration rate was calculated using the MDRD formula for SI units in patients of African origin at https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/adults-si-unit/Pages/adults-SI-units.aspx.

Statistical analyses were performed using SPSS 23 (IBM). Chi square (exact, 2-tailed) was used to analyze categorical variables, and analysis of variance was used to compare normally distributed continuous variables across treatment groups and study sites. The distribution of non-normally distributed continuous variables was assessed by the Kruskal–Wallis test.

Institutional ethical approval was obtained from all sites. All study participants also gave an informed written consent.

RESULTS

There were 105 patients enrolled; results are presented for the 94 patients who completed the study; of those, 42 were allocated to UC and 52 to PhysRx. Table 2 shows characteristics of the participants by treatment assignment. Characteristics by study site are shown in online Supplementary Material. Participants at the Nigerian site were all members of the Yoruba tribe; in Kenya, 30 were from the Kikuyu tribe, 7 Luo tribe and 3 Kisii tribe, and in South Africa participants were Xhosa or "Coloured" (the official census designation in South Africa); a mixture of white, Malay, Xhosa, and Khoisan.

Baseline blood pressures were not significantly different by treatment group but were significantly lower at followup with PhysRx (Table 2). Patients at the Nigerian site were older and had higher baseline systolic pressures and lower diastolic pressures (Table 3; Figures 1 and 2).

Renal function (estimated glomerular filtration rate) was not different between treatment groups (Table 2) but was significantly worse at the Nigerian site (Table 3). There were 17 patients with estimated glomerular filtration rate <60 (of which 13 were in Nigeria, 3 in Kenya, and 1 in South Africa). Seven patients had estimated glomerular filtration rate <50 (5 in Nigeria and 2 in Kenya).

Table 2. Characteristics of the study population by treatment assignment

	Usual care *n* = 42	Physiological *n* = 52	*P*
Normally distributed continuous variables, mean ± SD			**ANOVA**
Age (years)	56.36 ± 15.53	56.7 ± 13.25	0.66
Aldosterone ng/dl	19.87 + 14.49	23.22 + 15.82	0.30
Baseline BPSys	172.00 ± 20.48	169.95 ± 18.20	0.61
Baseline BPDias	84.28 ± 17.49	86.71 ± 24.76	0.61
1 year BPSys	152.58 ± 12.33	139.38 + 17.35	0.0001
1 year BPDias	89.56 ± 7.02	84.03 ± 10.99	0.009
Creatinine mmol/l	93.72 ± 28.59	95.38 ± 40.30	0.83
eGFR ml/min/1.73 m^2	87.33 ± 26.17	82.97 ± 30.13	0.48
Glucose mmol/l	6.95 ± 4.16	6.62 ± 3.51	0.68
Potassium mEq/l	4.12 ± 0.60	4.10 ± 0.60	0.94
Urine Na/creatinine	18.21 ± 12.08	17.78 ± 13.45	0.88
Skewed variables, median + interquartile range			*P* (Kruskal–Wallis)
PRA (ng/ml.hr)	7.1 ± 14.80	3.6 ± 7.58	0.85
Aldo/renin ratio	3.46 ± 7.68	3.60 ± 4.58	0.77
Categorical variables, %			Chi square
Male	52.8	43.1	0.24
Diabetic	11.1	17.2	0.13

Abbreviations: ANOVA, analysis of variance; BP Dias, diastolic blood pressure in mm Hg; BPSys, systolic blood pressure; eGFR, estimated glomerular filtration rate; PRA, plasma renin activity.

Table 3. Blood pressures at baseline and followup and classes and number of medication at baseline and followup by treatment group and by site; age, estimated glomerular filtration rate, and blood pressures by site

	Usual care, *n* = 42		Individualized therapy, *n* = 52	*P* (Chi square)
ACEi baseline	80.6%		77.6%	0.47
ACEi followup	47.2%		31.0%	0.09
Amiloride baseline	8.3%		8.6%	0.64
Amiloride followup	2.8%		19.0%	0.02
ARB baseline	8.3%		17.2%	0.18
ARB followup	11.1%		19.0%	0.24
CCB baseline	75.0%		87.9%	0.09
CCB followup	80.6%		74.1%	0.33
Diuretic baseline	80.6%		96.6%	0.02
Diuretic followup	100.0%		96.6%	0.38
Other medication* baseline	2.8%		0.0%	0.38
Other medication* followup	27.8%		13.8%	0.08
Spironolactone baseline	0.0%		15.5%	0.01
Spironolactone followup	44.4%		44.8%	0.57
	Mean ± SD			ANOVA
Baseline number of meds	1.81 ± 0.67		2.16 ± 0.56	0.007
Followup number of meds	3.14 ± 0.72		2.98 ± 0.98	0.41
	Nigeria	Kenya	South Africa	
Baseline number of meds	2.03 ± 0.48	1.69 ± 0.54	2.02 ± 0.62	0.0001
Followup number of meds	3.66 ± 0.67	2.47 ± 0.51	3.04 ± 0.89	0.0001
Age (years)	63.5 ± 12.37	53.22 ± 13.82	51.41 ± 13.39	0.001
eGFR ml/min/ 1.73 m^2	67.87 + 23.28	98.62 + 28.08	95.97 + 23.37	0.0001
Baseline BPSys	177.43 ± 19.39	165.13 ± 15.81	166.73 ± 19.64	0.01
Baseline BPDias	71.90 ± 18.86	96.13 ± 8.01	95.95 ± 28.04	0.0001
Followup BPSys	141.95 ± 15.32	155.44 ± 12.01	132.95 ± 16.49	0.0001
Followup BPDias	85.20 ± 9.0	91.19 ± 5.61	80.55 ± 13.11	0.0001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ANOVA, analysis of variance; ARB, angiotensin receptor blocker; BPSys, systolic blood pressure; BP Dias, diastolic blood pressure in mm Hg; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; Meds, blood pressure medications; Other medication*, sympatholytics including methyldopa, beta-adrenergic blockers and alpha-adrenergic blockers.

In the overall study population, control of both systolic and diastolic pressures was obtained in 11.1% of UC vs. 50.0% of PhysRx ($P = 0.0001$). Systolic control was achieved in 13.9% of UC vs. 60.3% of PhysRx ($P = 0.0001$); diastolic control in 36.1% of UC vs. 67.2 PhysRx, vs. ($P = 0.003$). Control was significantly worse in Kenya, for reasons discussed below. In Kenya, systolic control was obtained in only 12.5% of UC vs. 12.5% in PhysRx ($P = 0.70$), diastolic control in 25% vs. 53% ($P = 0.07$), and control of both in 6.3% vs. 6.3% ($P = 0.76$). When only the sites in Nigeria and South Africa were considered, systolic control was obtained in 15.0% of UC vs. 78.6% of PhysRx ($P < 0.0001$), diastolic control in 45.0% vs. 71.4% ($P = 0.04$), and control of both in 15.0% vs. 66.7% ($P = 0.0001$). If only the Nigerian site (where patients were randomized to the 2 treatment strategies) is considered, systolic control was obtained in 15% of UC vs. 85% of PhysRx ($P = 0.0001$), diastolic control in 45% vs. 75% ($P = 0.11$) and control of both systolic and diastolic pressure in 15% vs. 75% ($P < 0.0001$) even though the renal function was worse at that site.

Participants in the UC group were prescribed fewer medications at baseline, but there was no difference in the number of medications between groups at followup (Table 3). However,

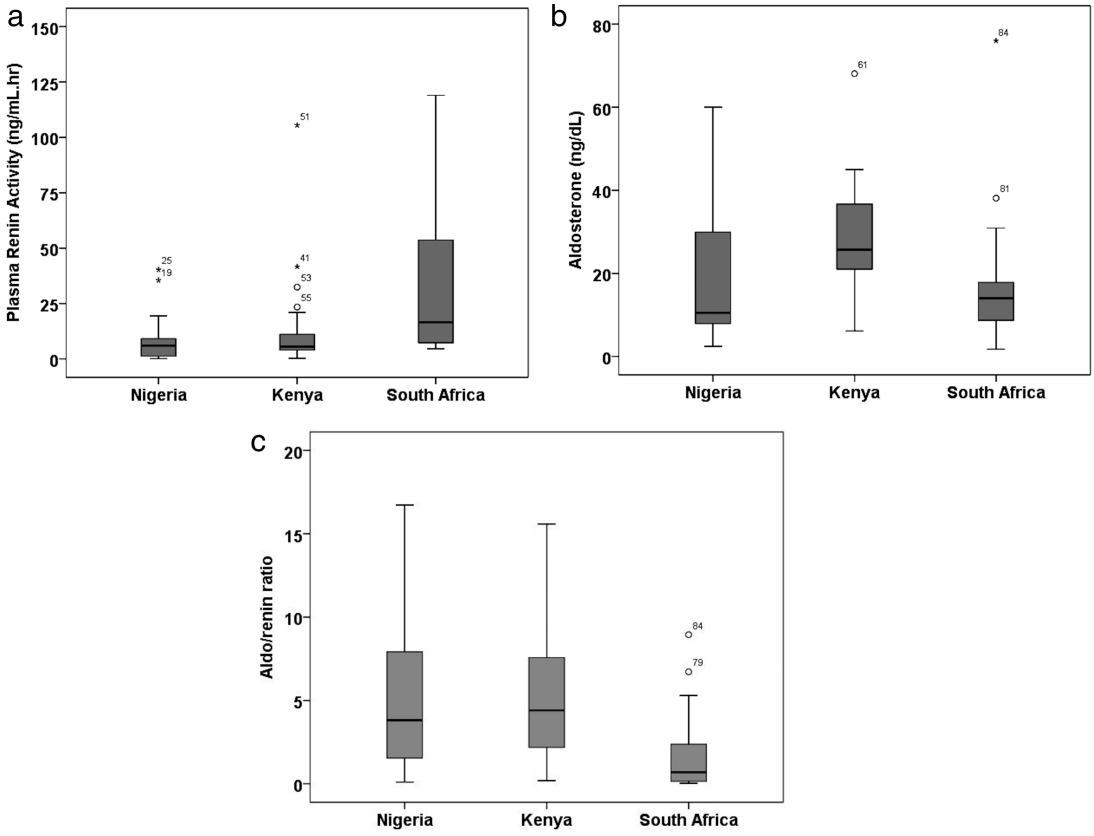

Figure 1. Boxplots of plasma aldosterone, plasma renin activity, and aldosterone/renin ratio by study site. (**a**) Plasma renin activity ($P = 0001$), and (**b**) aldosterone ($P = 0.017$) were significantly different across the sites; (**c**) aldosterone/renin ratio was not ($P = 0.29$); ANOVA. There appeared to be more participants with a Liddle phenotype in Nigeria and more with a primary aldosteronism phenotype in Kenya than in South Africa. (The higher percentage of Liddle phenotype in South Africa was likely masked by diuretic use at the time of renin/aldo sampling.). Abbreviation: ANOVA, analysis of variance.

there were important differences across sites. Patients in Kenya received fewer medications and those in Nigeria received more medications, particularly at followup (Supplementary eTable 3). The number of visits to the hypertension clinic was not different between treatment groups: 6.50 ± 3.26 in UC vs. 6.17 ± 2.87 in Physiological Rx ($P = 0.61$). However, there were significant differences in the number of visits at the 3 sites: Nigeria 8.23 ± 3.36, Kenya 4.56 ± 1.46, South Africa 5.32 ± 1.84 ($P < 0.0001$).

There were also important differences in plasma renin and aldosterone across the sites, and in urine Na/creatinine ratio (Table 2). Aldosterone levels were highest in Kenya, where sodium intake was the lowest, and there were more patients in both Nigeria and Kenya with phenotypes suggesting primary aldosteronism; in South Africa, more patients had a Liddle phenotype. There were no significant differences by treatment group (Table 4; Figure 2).

Medications at baseline and followup are shown in Supplementary eTable 3. The important differences between the randomized treatment groups were in prescription of amiloride. Spironolactone was prescribed more during the study in both treatment groups. As prescribed in the algorithm, amiloride was more likely to be prescribed for a phenotype suggesting Liddle syndrome.

During the course of the study, 2 participants at the Nigerian site went on to dialysis; of those, 1 died of renal failure; 1 participant in South Africa died of postoperative sepsis following surgery for metastatic cancer and biliary obstruction. Their characteristics are described in online Supplementary eTable 13. No participant had a stroke, myocardial infarction, or heart failure.

DISCUSSION

We found that personalized medicine based on phenotyping by levels of PRA and aldosterone significantly improved blood pressure control among Black Africans. In Nigeria and South Africa, the algorithm markedly improved blood pressure control, even though the patients allocated to PhysRx had more resistant hypertension at baseline. The higher number of medications at followup suggest that efforts to control blood pressure were more strenuous at the Nigerian site, where the percent of patients achieving control was best despite having worse renal function.

An important limitation was that participants at the South African site were not randomized; they were all allocated to PhysRx. (It took so long to obtain governmental approval to use amiloride that the investigators forgot they were to randomize the patients, and the budget did not permit travel to monitor the sites.) In a way this worked, out, as there was no selection bias (all the patients at that site were allocated to

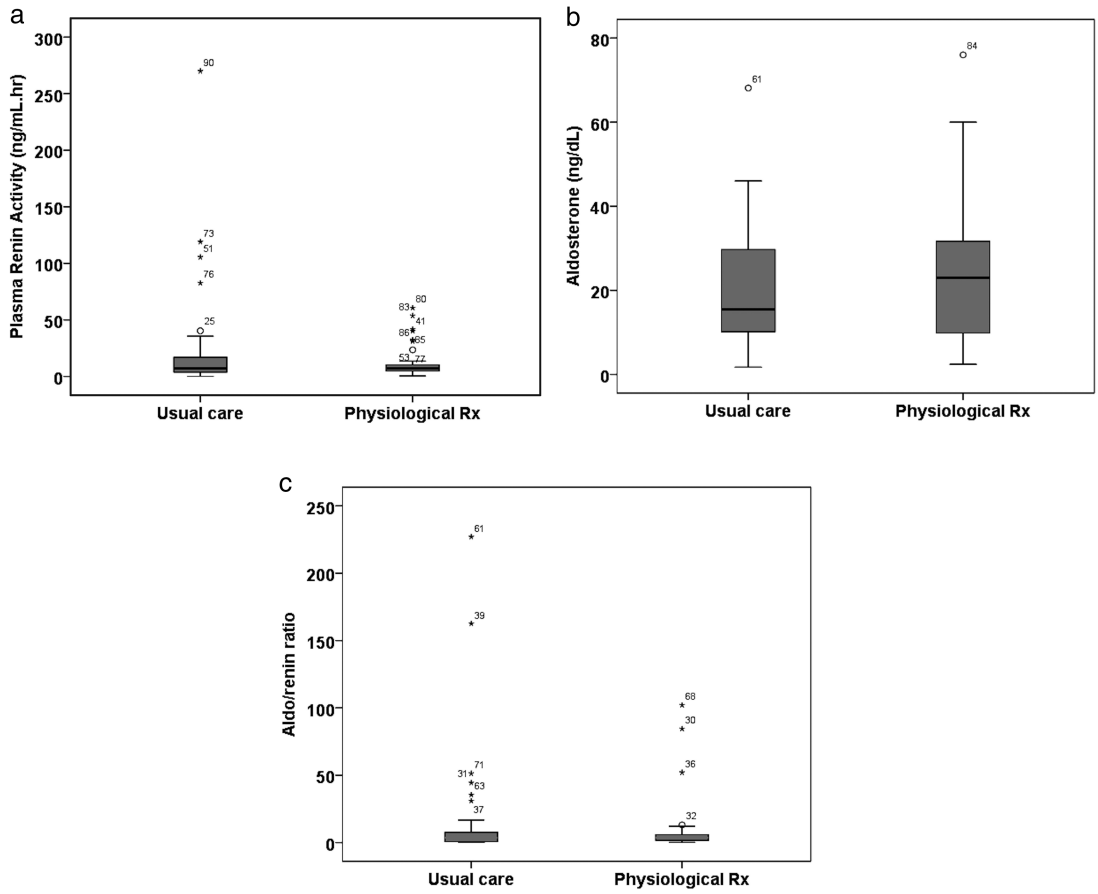

Figure 2. Boxplots of (**a**) plasma renin activity, (**b**) plasma aldosterone, and (**c**) aldosterone/renin ratio by treatment group. There were no significant differences between treatment groups in plasma renin activity, plasma aldosterone, or aldosterone/renin ratio.

Table 4. Phenotypes by treatment group, defined by tertiles of plasma renin and aldosterone

Phenotype	Usual care (%)	Physiologically individualized (%)	*P*
Liddle	11.9	13.5	0.96
Primary aldosteronism	11.9	9.6	
Renal	9.5	7.7	
Other	44.7	55.3	

Tertiles of plasma renin activity (PRA) and plasma aldosterone (Aldo) were used to define the phenotypes because the samples were obtained while patients were taking their baseline medications. Liddle syndrome was defined by PRA and Aldo in the lowest tertile; primary aldosteronism by Aldo in the highest tertile with PRA in the lowest; renal by both PRA and Aldo in the highest tertile; others were the remainder. PRA tertiles were <4.7, 4.7 to 9, and ≥9 ng/ml.hr; Aldo tertiles were <105, 105 to 270, and >270 pg/ml.

PhysRx), and they had to stop recruitment when the granting agency required unspent funds to be returned after the long delay, so the number of patients allocated to UC and PhysRx was nearly balanced (n = 42 UC, 52 PhysRx). The Nigerian site used more drugs such as methyldopa and beta-blockers and the South African site (which had more patients with the Liddle phenotype) used more amiloride; nevertheless as reported, the results within the Nigerian site alone (which randomized the patients) showed a significant improvement in blood pressure control: systolic control was obtained in 15% of UC vs. 85% of PhysRx (P = 0.0001), diastolic control in 45% vs. 75% (P = 0.11) and control of both systolic and diastolic pressure in 15% vs. 75% (P < 0.0001).

Reasons for the poor control of blood pressure in the Kenya study site probably include inability to pay for blood pressure medications, and fewer clinic visits. The poor control at the Kenyan site (at Nakuru) was similar to that reported from a hypertension clinic in Nairobi, Kenya.[23] In that clinic only 25% of all patients had their pressure controlled, and in this study we selected patients whose pressure was not controlled by UC. It is possible that besides inability to pay for medication there may be other (perhaps cultural) reasons for nonadherence to medication in Kenya; in the Nairobi clinic report, nonadherence was significantly related to uncontrolled blood pressures but not to socioeconomic status.[23]

The motivation for this study was the observation by J.D.S. that patients from North Buxton, Ontario, a settlement established for escaped slaves from the United States who came to Canada *via* the Underground Railroad, were much more likely to have low levels of stimulated plasma renin, and much more likely to have familial primary aldosteronism,[2,13] with bilateral adrenocortical hyperplasia. Although <1% of patients in the clinic were Black, 4 of the first 10 patients

requiring adrenalectomy because their hypertension could not be controlled were Black; of these one was from Swaziland;[2] the other 3 were from North Buxton. It was precisely because there were so few Black patients in the clinic population that it was obvious their hypertension was different.

Besides an increase in the prevalence of primary aldosteronism, Black patients have variants of several genes affecting renal tubular absorption of sodium and water, largely through the renal tubular epithelial sodium channel.[9] Baker *et al.*[16] reported that in Black patients in London, UK (predominantly of Caribbean origin), 5% had a variant of Liddle syndrome (T594M) and responded selectively to amiloride. Rayner's group described a different variant of Liddle syndrome (R563Q),[24] which was present in 20% of the Khoi San people of the Kalahari desert, 9% of Nguni (Xhosa/Zulu) and in 6% overall of hypertensives in Cape Town.[25] While resident in the Kalahari desert carriers of this allele are not hypertensive, but they become severely hypertensive when they move to Cape Town, and respond selectively to amiloride.[25,26] A Liddle phenotype was present in 6% of patients attending a hypertension clinic at a Veterans' Administration hospital in Louisiana.[27]

Besides variants of true Liddle syndrome, there are several other genetic variants that affect renal tubular reabsorption of salt and water and lead to the Liddle phenotype. Spironolactone is often recommended for patients with resistant hypertension.[28] Saha *et al.*[29] reported a greater reduction of blood pressure with amiloride than with spironolactone among Black patients with low renin hypertension. "The reductions in systolic and diastolic blood pressures (mm Hg) were, respectively, 9.8 ± 1.6 (SE) and 3.4 ± 1.0 for amiloride ($P < 0.001$) and 4.6 ± 1.6 ($P = 0.006$) and 1.8 ± 1.0 for spironolactone ($P = \pm 0.07$)." In contrast, Lane *et al.* reported that amiloride 10 mg daily was less effective than spironolactone 25 mg daily.[30] It is likely that results could be improved by determining whether the patient has a Liddle phenotype, for which amiloride should be more effective, or a primary aldosterone phenotype, for which aldosterone antagonists should be more effective. The findings of Laffer *et al.*[31] support that hypothesis; they reported that a variant of CYP4A11, which activates the epithelial sodium channel, was resistant to spironolactone, but responsive to amiloride.

Among participants in this study, we selected for Sanger sequencing of candidate genes the most extreme 18 patients (the number of cases was limited by the funding available).[32] CYP11B2 was sequenced in 9 with the most extreme primary aldosteronism phenotype; SCNN1B, NEDD4L, GRK4, UMOD, and NPPA genes were sequenced in 9 cases with the most extreme Liddle phenotype. In the primary aldosteronism phenotype, there were 14 nonsynonymous variants (NSVs) of CYP11B2; out of 14, 9 variants were found in all 9 patients sequenced. There were 4 NSV of GRK4; at least one was found in all 9 patients. There were 3 NSV of SCNN1B. NPPA was found to have 1 NSV and NEDD4L did not have any variants. UMOD had 3 NSV.[32] Thus among these Black African patients with uncontrolled hypertension there were many genetic variants predisposing to primary aldosteronism or to salt and water retention due to variants affecting renal tubular function.

Although some hypertension guidelines specify that if patients are not controlled by UC, investigation should be carried out to identify secondary hypertension. However, many/most physicians do not do this; the term "diagnostic inertia" has been used to differentiate this cause of resistant hypertension from "therapeutic inertia", the failure to prescribe more intensive therapy as indicated. For example, the Canadian guideline[33] recommends measurement of plasma renin and aldosterone to diagnose primary aldosteronism; however, there is no mention of Liddle syndrome, and amiloride is mentioned only as a cause of hyperkalemia. Neither Liddle syndrome nor amiloride is mentioned in the US guideline.[5] The literature cited above indicates that a Liddle phenotype is present in ~6% of patients with hypertension; in our African patients with uncontrolled hypertension it was 13.9%. Thus, more attention should be paid to the Liddle phenotype and to amiloride.

Our findings highlight the adverse consequences of diagnostic inertia,[20,34] and the advantages of measuring plasma renin and aldosterone not only to diagnose primary aldosteronism, but also renal tubular causes of salt and water retention (with a Liddle phenotype), so that appropriate therapy can be prescribed. Physiologically individualized therapy based on plasma renin/aldosterone phenotyping is a relatively inexpensive way to improve blood pressure control, and may have advantages over genome-based personalized medicine.

In conclusion, physiologically individualized therapy for resistant hypertension by phenotyping with plasma renin and aldosterone was associated with better blood pressure control in Black African patients with uncontrolled hypertension. This approach should be tested in African Americans, as previously suggested,[8] and in patients of any race with resistant hypertension.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURE

Dr Jones has performed contract research in the past 2 years with Eli Lilly, Otsuka, Bayer, and ZS Pharma. She has received lecture honoraria from Bonitas Medical Aid. Dr Rayner has received grants from the National Research Foundation and Medical Research Council of South Africa. In the past 2 years he has received lecture honoraria/consulting fees from Servier, Novartis, Merck, Boehringer-Ingelheim, and Cipla and has performed contract research with Otsuka, Novartis, Eli Lilly, Takeda, Boehringer-Ingelheim, and Merck. He is a member of the Editorial Boards of Cardiovascular Journal of South Africa, Nephron Clinical

Practice and Austen Hypertension. Dr Spence has received grants from the Canadian Institutes for Health Research, the Heart & Stroke Foundation of Canada, and NIH/NINDS. In the past 2 years he has received lecture honoraria/consulting fees from Bayer and Bristol Myers Squibb, and has performed contract research with Pfizer, Bayer, Bristol Myers Squibb, Acasti Pharma, POM Wonderful, CVRx, and Gore. He is an officer and shareholder of Vascularis Inc. He is a member of the Editorial Boards of Hypertension, Stroke, Arteriosclerosis, Thrombosis & Vascular Biology, Canadian Journal of Cardiology, Cerebrovascular Diseases, and Stroke & Vascular Neurology. He also receives royalties on books from Vanderbilt University Press and McGraw-Hill Medical publishers. All other authors declared no conflict of interest.

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