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ORIGINAL ARTICLE

Heart rate variability on antihypertensive drugs in Black patients living in sub-Saharan Africa

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Abstract

Background. Compared with Caucasians, African Americans have lower heart rate variability (HRV) in the high-frequency domain, but there are no studies in Blacks born and living in Africa. *Methods.* In the Newer versus Older Antihypertensive agents in African Hypertensive patients trial (NCT01030458), patients (30–69 years) with uncomplicated hypertension (140–179/90–109 mmHg) were randomized to single-pill combinations of bisoprolol/hydrochlorothiazide (R) or amlodipine/valsartan (E). 72 R and 84 E patients underwent 5-min ECG recordings at randomization and 8, 16 and 24 weeks. HRV was determined by fast Fourier transform and autoregressive modelling. *Results.* Heart rate decreased by 9.5 beats/min in R patients with no change in E patients (−2.2 beats/min). R patients had reduced total (−0.13 ms²; $p = 0.0038$) and low-frequency power (−3.6 nu; $p = 0.057$), higher high-frequency (+3.3 nu; $p = 0.050$) and a reduced low- to high-frequency ratio (−0.08; $p = 0.040$). With adjustment for heart rate, these differences disappeared, except for the reduced low-frequency power in the R group (−4.67 nu; $p = 0.02$). Analyses confined to 39 R and 47 E patients with HRV measurements at all visits or based on autoregressive modelling were confirmatory. *Conclusion.* In native Black African patients, antihypertensive drugs modulate HRV, an index of autonomous nervous tone. However, these effects were mediated by changes in heart rate except for low-frequency variability, which was reduced on beta blockade independent of heart rate.

Key Words: *Antihypertensive drugs, Blacks, heart rate variability, randomized clinical trial, sub-Saharan Africa*

Introduction

The autonomic nervous system plays a role in the pathogenesis of hypertension. Increased sympathetic activity or a decreased parasympathetic activity contribute to the development and maintenance of high blood pressure (1). Measurement of heart rate

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variability (HRV) in the frequency domain provides information on how the autonomous nervous system controls the cardiovascular system (2). Indeed, the high- and low-frequency components of HRV respectively reflect the activity of the parasympathetic and sympathetic nervous system. The low- to high-frequency ratio is a measure of sympatho-vagal balance (3,4).

In subjects at risk of hypertension and in hypertensive patients, the high-frequency component of HRV is generally reduced (5). Reduced HRV predicts all-cause mortality (6) and cardiac events (7). Moreover, compared with Caucasians, African Americans have an increased prevalence of hypertension and reduced HRV (8–14). Changes in sympathetic modulation of the cardiovascular system might therefore be a risk factor for cardiovascular complications (1,6,7,15,16), which might be reversible by blood-pressure lowering treatment. However, to our knowledge, no study addressed the role of the autonomic nervous system in cardiovascular regulation in Black hypertensive patients born and living in Africa. We addressed this issue in the Newer versus Older Antihypertensive Agents in African Hypertensive Patients trial (NOAAH; NCT01030458), of which the protocol (17) and main results (18) were reported elsewhere. The current article reports on changes in HRV on randomized treatment with older and newer drugs in native African hypertensive patients.

Methods

The NOAAH trial was an open, randomized, investigator-led multicentre study complying with the guidelines for good clinical practice (19). Six centres located in Cameroon ($n = 2$), Gabon ($n = 1$), Nigeria ($n = 2$) and Senegal ($n = 1$) enrolled patients. The sponsor (Hypertension Unit, University of Kinshasa Hospital, Democratic Republic of Congo) and all participating centres obtained ethical clearance from their local institutional review boards and/or national regulatory authorities. Patients provided written or witnessed informed consent at screening.

As outlined in detail in the published protocol (17), treatment-naïve or previously treated patients of either sex, aged 30–69 years with uncomplicated grade-1 or grade-2 hypertension and a maximum of two additional risk factors qualified for enrolment. Previously treated patients should not have a compelling indication to continue treatment and should be on a single drug. After a 4-week run-in period off treatment, eligible patients had a sitting blood pressure ranging from 140 to 179 mmHg systolic or from 90 to 109 mmHg diastolic, or both, while systolic blood pressure measured immediately after standing up had to be at least 110 mmHg. These blood pressure thresholds were averages of three consecutive readings obtained by means of validated (20) Omron 705IT monitors (Omron Healthcare Co., Ltd., Kyoto, Japan) fitted with a cuff adjusted to arm circumference. In addition to major illness and high cardiovascular risk, the exclusion criteria encompassed: atrial fibrillation, electrocardiographic left ventricular hypertrophy with strain pattern, a serum creatinine concentration, higher than 1.4 mg/dl in women or 1.5 mg/dl in men, and proteinuria or haematuria on a dipstick urine test.

The Study Coordinating Centre (SCC) in Leuven randomized eligible patients to a single-pill combination of either 6.25 mg hydrochlorothiazide plus 5 mg bisoprolol (older drugs) or valsartan 160 mg plus amlodipine 5 mg (newer drugs). To achieve blood pressure control, the dose of bisoprolol or amlodipine in the single-pill combination could be doubled to 10 mg. In the two treatment groups, if blood pressure remained uncontrolled, α-methyldopa could be added to the study medication.

At randomization and at 8, 16 and 24 weeks of follow-up, investigators record standard 12-lead ECGs by means of the paperless Cardiax device. HRV was measured from 5-min ECG recordings, using the Cardiax software (version 3.50.2, International Medical Equipment Developing Co. Ltd., Budapest, Hungary). The Cardiax software computes the power spectrum in the frequency domain by fast Fourier transform and by autoregressive modelling and provides the low-frequency (0.04–0.15 Hz) and high-frequency (0.15–0.40 Hz) components of HRV in milliseconds and the low- to high-frequency ratio. Normalized units (nu) of low- and high-frequency powers were calculated as the low- and high-frequency powers divided by the difference (total power − very low-frequency power) × 100.

The SAS software (SAS Institute, Cary, NC, USA), version 9.3, was used for database management and statistical analysis. The normality of continuously distributed variables was evaluated by the Kolmogorov–Smirnov statistic. Skewness and kurtosis were computed as the third and fourth moments about the mean (Supplementary Figures 1 and 2, to be found online at http://informahealthcare.com/doi/abs/10.3109/08037051.2013.836810). Non-normally distributed variables were log-transformed. The main analysis included all randomized patients with at least one follow-up visit according to the intention-to-treat principle. The cohort analysis only included patients who had HRV measured at each scheduled visit. Means were compared by Student's *t*-test for paired or unpaired data as appropriate and proportions by the χ^2 statistic. A mixed model was applied to assess treatment effects on HRV with the baseline values and follow-up time as fixed effects and centre as random effect. In sensitivity analyses, models also included heart rate as a covariable. Statistical significance was a two-sided *p*-value of 0.05.

Results

Of 294 screened patients, 271 were enrolled in the run-in period and 183 were randomized: 89 and 94 to old and new drugs, respectively (Figure 1). In the old and new drug groups, respectively, 57 and 67 completed the 6-month follow-up, 10 and nine patients defected from follow-up for undocumented reasons, and 22 and 18 withdrew from the study (Figure 1). Of the 89 and 94 patients randomized to old and new drugs, 72 and 84 had at least one measurement of HRV after randomization and were included in the present analysis.

Table I shows there were no between-group differences in the baseline characteristics among all analysed patients ($p \geq 0.06$) as well as among those in the cohort analysis ($p \geq 0.09$) with the exception of waist circumference ($p = 0.04$) and diastolic blood pressure ($p = 0.015$). The analysis included 83 (53.2%) women and 105 (67.3%) treatment-naïve patients. Age ($\pm$ SD) averaged 51.5 ± 8.9 years, ranging from 30.5 to 68.9 years. Blood pressure at randomization was 156.2 ± 11.5 mmHg systolic and 92.3 ± 10.1 mmHg diastolic. Total, low-frequency and high-frequency power averaged 4.29 ± 0.37 log ms^2, 43.6 ± 18.1 nu, and 20.02 ± 14.42 nu and the low-to-high-frequency ratio was 0.40 ± 0.36 log. Patients included or not included in the cohort analysis had similar baseline characteristics ($p \geq 0.09$).

Women compared with men had higher normalized high-frequency power (22.2 vs 17.5 nu; $p = 0.041$) and therefore lower low- to high-frequency ratio (0.33 vs 0.48; $p = 0.013$). Log total power was inversely correlated with age ($r = 0.20$; $p = 0.013$). The correlations coefficients with heart rate were 0.15 ($p = 0.057$) for log total power, -0.06 ($p = 0.43$) for normalized low-frequency power, -0.19 ($p = 0.016$) for normalized high-frequency power and 0.14 ($p = 0.073$) for the low- to high-frequency ratio.

During follow-up, heart rate decreased by 9.5 beats/min on old drugs, with no change in patients (-2.2 beats/min) on new drugs, resulting in a baseline-adjusted between-group difference of 7.3 beats/min (Table II; Figure 2). On old drugs, log total power

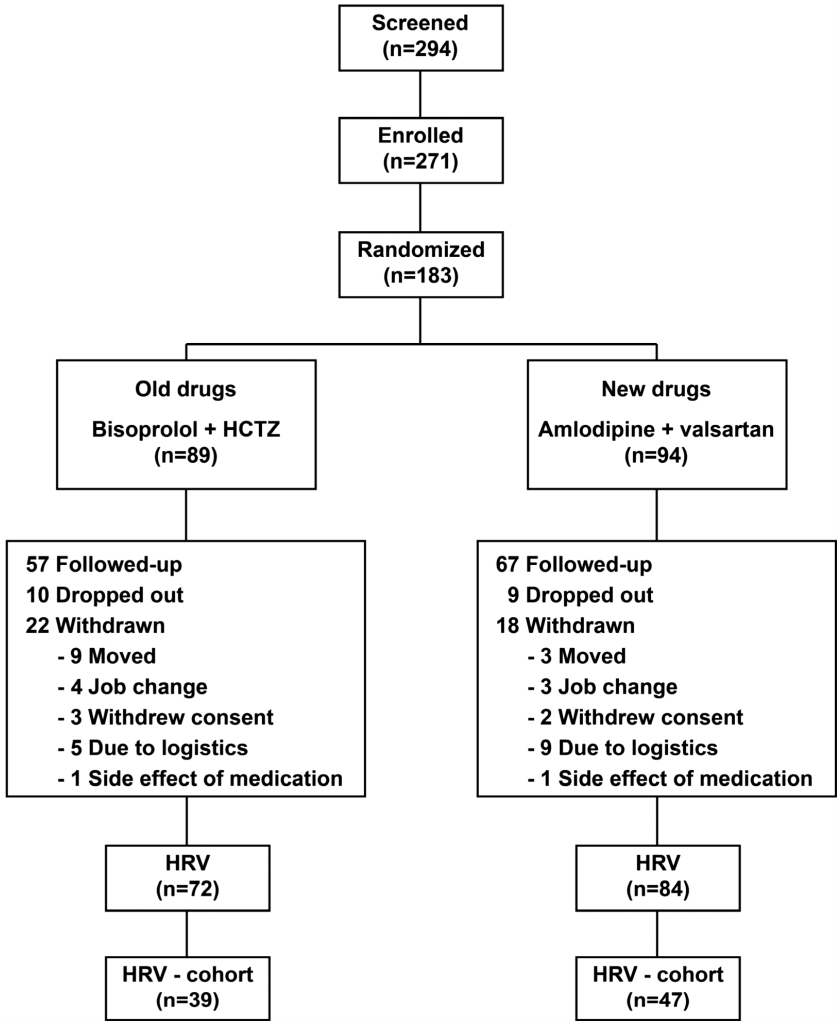

Figure 1. Flow diagram of patients. Logistical reasons included delayed replenishment of the local supply of study medications and internet or computer failures at local centres. HCTZ, hydrochlorothiazide. HRV refers to patients, who had at least one measurement of heart rate variability after randomization. Cohort refers to patients with all scheduled visits available for analysis.

Table I. Baseline characteristics by type of analysis and randomization group.

Characteristic	Type of analysis			
	All patients		Cohort	
Randomization	Old	New	Old	New
Number (%) with characteristic				
All patients in category	72	84	39	47
Women	37 (51)	46 (55)	24 (62)	24 (51)
Smokers	5 (7)	1 (1)	1 (3)	0 (0)
Drinking alcohol	22 (31)	25 (30)	11 (28)	18 (38)
Treatment naïve	49 (68)	56 (67)	26 (67)	28 (60)
Mean ± SD of characteristic				
Age, years	51.7 ± 8.2	51.4 ± 9.5	52.7 ± 7.6	50.9 ± 9.1
Body mass index (kg/m^2)	28.7 ± 4.7	27.6 ± 4.9	28.9 ± 4.9	27.5 ± 4.4
Waist circumference (cm)	95.2 ± 11.5	93.4 ± 11.3	97.6 ± 11.2	92.8 ± 10.4
Sitting measurements of				
Systolic pressure (mmHg)	155.9 ± 10.4	156.5 ± 12.5	157.3 ± 11.1	153.2 ± 11.1
Diastolic pressure (mmHg)	92.6 ± 9.8	92.1 ± 10.5	95.4 ± 9.4	90.6 ± 8.5
Heart rate (beats/min)	70.4 ± 10.8	70.4 ± 9.4	71.8 ± 9.1	71.0 ± 10.6
Heart rate variability measurements				
Total power (log ms^2)	4.29 ± 0.35	4.28 ± 0.38	4.32 ± 0.34	4.25 ± 0.34
(geometric mean)	(19,561)	(19,116)	(21,111)	(17,824)
Low-frequency power (nu)	41.8 ± 19.8	45.2 ± 16.5	41.9 ± 20.9	48.6 ± 15.6
High-frequency power (nu)	18.8 ± 14.3	21.1 ± 14.5	20.0 ± 16.2	19.6 ± 13.6
Low- to high-frequency ratio, log	0.41 ± 0.37	0.39 ± 0.35	0.41 ± 0.42	0.46 ± 0.33
(geometric mean)	(2.59)	(2.45)	(2.56)	(2.88)

The overall analysis encompasses patients with at least one measurement of heart rate variability after randomization and the cohort analysis patients with all scheduled visits available for analysis. Old and new refer to single-pill combinations of hydrochlorothiazide plus bisoprolol and valsartan plus amlodipine. Measurements of blood pressure are averages of three consecutive readings in the sitting position. Heart rate variability was analysed using fast Fourier transform. Between-group differences in the baseline characteristics among all patients ($p \geq 0.06$) and among those in the cohort analysis ($p \geq 0.09$) were not significant with the exception of waist circumference ($p = 0.04$) and diastolic blood pressure ($p = 0.015$) in the cohort analysis.

decreased by − 0.20 ms^2 ($p = 0.0003$), high-frequency power increased by 7.1 nu ($p = 0.0020$) and the low- to high-frequency ratio on the log scale decreased by 0.15 ($p = 0.0054$), with no change in low-frequency power (− 1.0 nu; $p = 0.70$). The corresponding within-group changes in the new-drug group were all non-significant ($p \geq 0.22$). As a result (Table II), the baseline-adjusted between-group differences (new minus old drugs) amounted to 3.4%, 3.6 nu, − 3.3 nu and 21.2% for total power, low- and high-frequency power, and the low- to high-frequency ratio, respectively. With adjustment for heart rate, these between-group differences disappeared ($p \geq 0.22$), except for the decreased low-frequency power in the old-drug group (− 4.67 nu; $p = 0.02$). Analyses additionally adjusted for sex and age, or confined to patients with HRV available at all visits, or based on autoregressive modelling (Supplementary Tables I and II; Supplementary Figure 3 to be found http://informahealthcare.com/doi/abs/10.3109/08037051.2013.836810) were confirmatory.

Table II. Changes in heart rate and heart rate variability by randomization group.

Characteristic	Old	New	Δ (CI)	p
Number	72	84		
Heart rate measurements				
Heart rate (beats/min)	− 9.5 ± 1.6‡	− 2.2 ± 1.4	7.3 (5.6 to 9.4)	< 0.0001
Total power (log ms^2)	− 0.20 ± 0.06‡	− 0.06 ± 0.05	0.13 (0.04 to 0.22)	0.0038
(percent)	− 4.7	− 1.29	3.4 (1.0 to 5.7)	
Low-frequency power (nu)	− 1.0 ± 2.7	− 0.4 ± 2.2	3.6 (− 0.08 to 7.4)	0.057
High-frequency power (nu)	7.1 ± 2.3†	2.4 ± 2.0	− 3.3 (− 6.6 to − 0.02)	0.050
Low- to high-frequency ratio	− 0.15 ± 0.05†	− 0.06 ± 0.05	0.08 (0.01 to 0.15)	0.040
(percent)	− 36.6	− 15.4	21.2 (2.7 to 39.8)	

The overall analysis encompasses patients with at least one measurement of heart rate variability after randomization. Heart rate variability was analysed using fast Fourier transform. Within-group changes (follow-up minus baseline) are mean ± SE. Δ (CI) refers to the baseline-adjusted differences 95% confidence interval) of the treatment effects (new minus old). p-values were computed using a mixed model. Significance of the within-group changes: *$p \leq 0.05$; †$p \leq 0.01$; ‡$p \leq 0.001$.

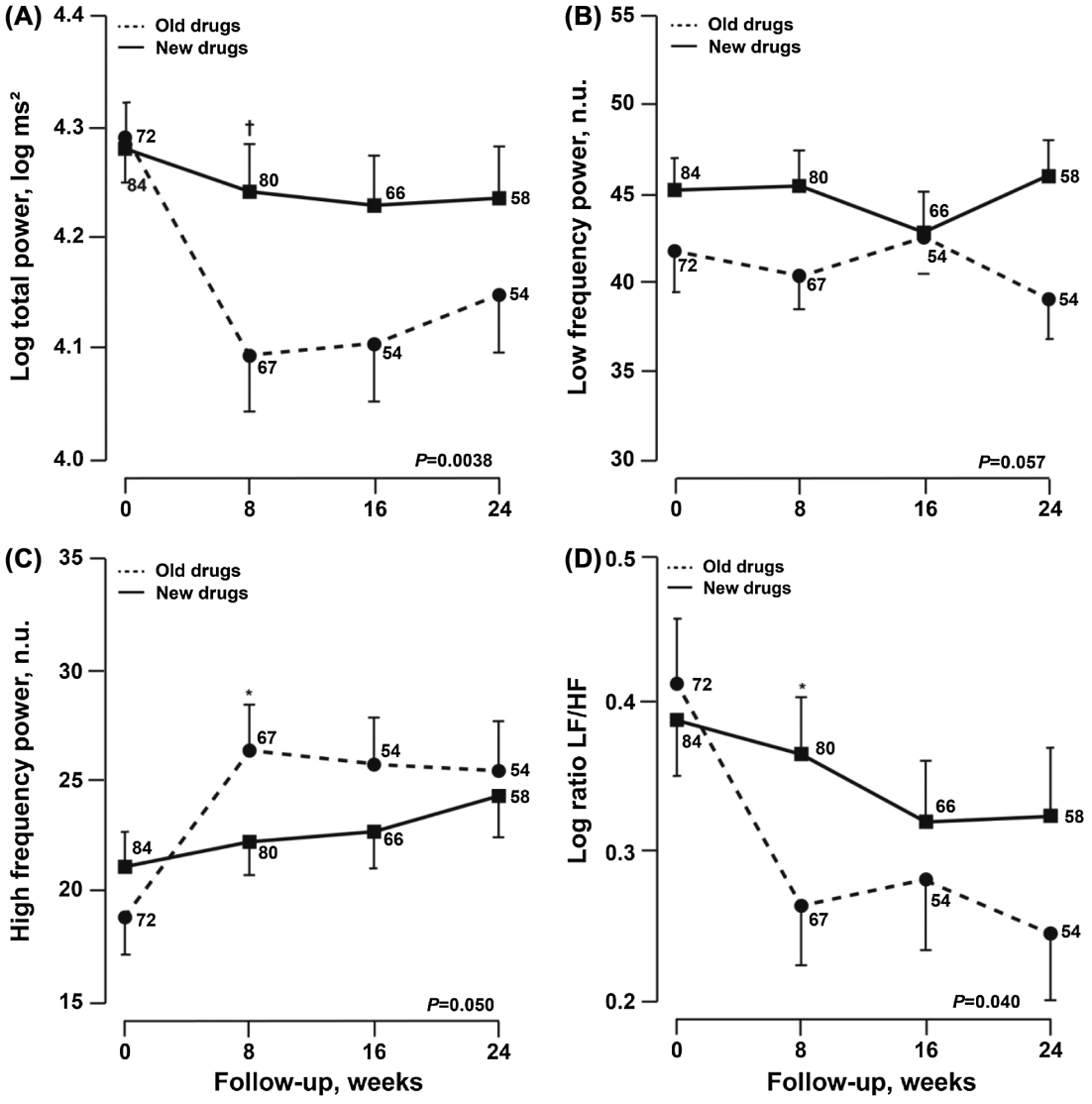

Figure 2. Total power (A), low-frequency power (B), high-frequency power (C) and low- to high-frequency ratio (D) at randomization and during follow-up in patients randomized to old drugs ($n = 72$) or new drugs ($n = 84$). Heart rate variability was analysed using fast Fourier transform. Plotted values are means ± SE. The number of patients contributing to the means is given. p values denote the significance of the between-group differences derived from a mixed model. Significance of the between-group differences at individual visits: $^{*}p \leq 0.05$; $^{\dagger}p \leq 0.01$; $^{\ddagger}p \leq 0.001$.

Discussion

In this randomized clinical trial conducted in native Black African patients, treatment with a single-pill combination containing hydrochlorothiazide plus bisoprolol, compared with the combination of valsartan plus amlodipine reduced total and low-frequency power, increased high-frequency power and therefore decreased the low-to-high-frequency ratio. The between-group differences in total power, high-frequency power and the high- to low-frequency ration disappeared when adjusted for the lower heart rate in patients receiving the beta-blocker bisoprolol. The key finding of our study was that independent of heart rate low-frequency power remained suppressed in patients randomized to the combination including bisoprolol.

Bisoprolol is a selective β_1-adrenoceptor antagonist that does not have intrinsic sympathomimetic (partial agonist) or membrane stabilizing (local anaesthetic) activity (21). Bisoprolol does not have any clinically relevant effects on the pharmacokinetics of hydrochlorothiazide or vice versa. Both β_1- and β_2-adrenoceptors coexist in the atria of the human heart and are dynamically regulated in response to various physiological and pathological stimuli (22). The dynamically regulated interplay between both receptor types in the control of heart rate might explain why the low-frequency component of HRV remained lower in the old-drug compared with the new-drug group even after adjustment for heart rate. The absence of a correlation of the low-frequency component with heart rate would also support this hypothesis. Alternatively, cardioselective beta-blockers with lipophilic characteristics, such as bisoprolol penetrate the brain and might have effects on sympathetic modulation, for instance by indirectly

increasing vagal tone. This might also explain why the low-frequency component of HRV remained suppressed independent of heart rate.

Women compared with men had higher normalized high-frequency power and a lower low- to high-frequency ratio). These observations are in keeping with population data collected in the framework of the European Project on Genes in Hypertension (EPOGH). Among 858 participants (53.8% female), women compared with men had lower ($p < 0.001$) relative power in the low-frequency range (41.5 vs 48.8 nu) and lower mean low- to high-frequency ratio (0.06 vs 0.11, log), but higher relative power in the high-frequency range (47.4 vs 40.6 nu). In EPOGH participants, high-frequency power decreased with age ($r = -0.43$), whereas the low-frequency power increased ($r = 0.32$) (23). The small age range (30.5–68.9 years), selection of patients with hypertension and ethnic differences might explain the absence of these associations with age in our currents study.

Beta-blockers without intrinsic sympathomimetic activity, such as bisoprolol, decrease heart rate and cardiac output. Lower heart rate is associated with reduced HRV. The lesser decrease in systolic blood pressure on the old-drug combination (18) is probably the consequence of the beta–blocker-induced reduction of heart rate, which is responsible for a later return of the reflected waves in the central arteries during systole and more pronounced systolic augmentation (24,25). Furthermore, under treatment with inhibitors of the renin system, but not under treatment with beta–blockers, the structural arteriolar abnormalities associated with hypertension regress. The ensuing reduction of the reflection coefficients likely reduces the amplitude of the backward pressure wave and promotes a decrease of systolic blood pressure and pulse pressure in the brachial artery (26). Further studies should elucidate whether in addition to higher blood pressure level on the older drugs, reduced HRV, as suggested by the Framingham results (6,7), might contribute to the worse outcome on combinations of older vs newer drugs (27).

Our current results must be interpreted within the context of some potential limitations. First, we only derived measures of HRV from 5min ECG recordings. However, Kotecha and colleagues (15) reported that 5-min HRV can predict obstructive angiographic coronary disease. Second, low- and high-frequency powers are only approximate measures of sympathetic and parasympathetic tome, respectively. Third, our study was not designed to explore the mechanisms explaining why low-frequency power was reduced on bisoprolol independent of heart rate.

In conclusion, the present study was the first to assess HRV in Black hypertensive patients born and living in sub-Saharan Africa. Independent of heart rate, a reduced low-frequency power was observed in hypertensive patients randomized to antihypertensive drug treatment based on beta-blockade. This might be a harbinger of less reduction of cardiovascular risk compared with the newer drugs.

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Supplementary material available online

Supplementary Tables I and II
Supplementary Figures 1 to 3

Supplementary material for Osakwe CE, et al., Heart rate variability on antihypertensive drugs in Black patients living in sub-Saharan Africa, Blood Pressure, 2013; doi: 10.3109/08037051.2013.836810

Supplementary Table I. Heart rate variability based on autoregressive modelling by type of analysis and randomization group.

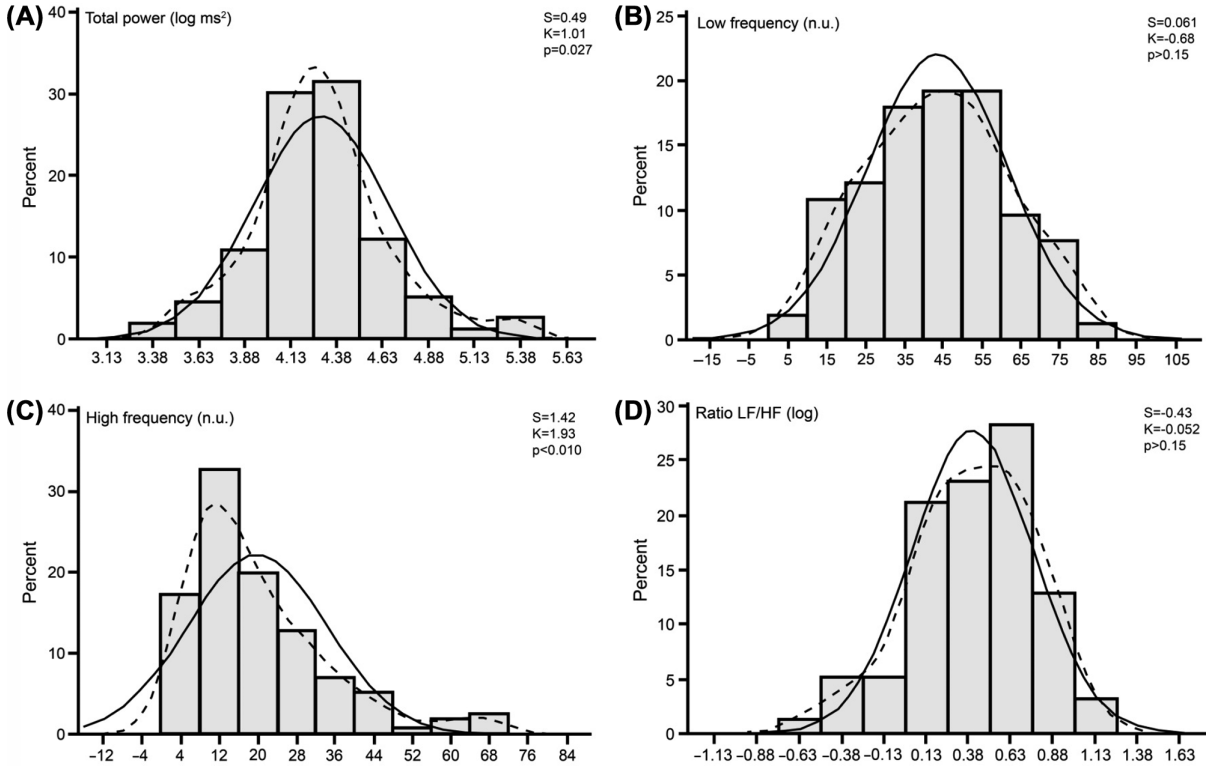
	Type of analysis			
	All patients		Cohort	
Characteristic Randomization	Old	New	Old	New
Number	72	84	39	47
Total power (log ms^2)	3.94 ± 0.33	3.96 ± 0.42	3.97 ± 0.31	3.93 ± 0.34
(Geometric mean)	8710	9120	9333	8511
Low-frequency power (nu)	42.5 ± 18.3	43.8 ± 15.5	45.5 ± 19.4	46.6 ± 13.9
High-frequency power (nu)	18.8 ± 14.3	20.3 ± 14.0	20.4 ± 16.7	19.3 ± 13.4
Low- to high-frequency ratio (log)	0.42 ± 0.37	0.40 ± 0.34	0.41 ± 0.42	0.45 ± 0.33
(Geometric mean)	2.63	2.51	2.57	2.81

The overall analysis encompasses patients with at least one measurement of heart rate variability after randomization and the cohort analysis patients with all scheduled visits available for analysis. Old and new refer to single-pill combinations of hydrochlorothiazide plus bisoprolol and valsartan plus amlodipine. Values are mean± SD. Between-group differences among all patients ($p \geq 0.50$) and among those in the cohort analysis ($p \geq 0.32$) were not significant.

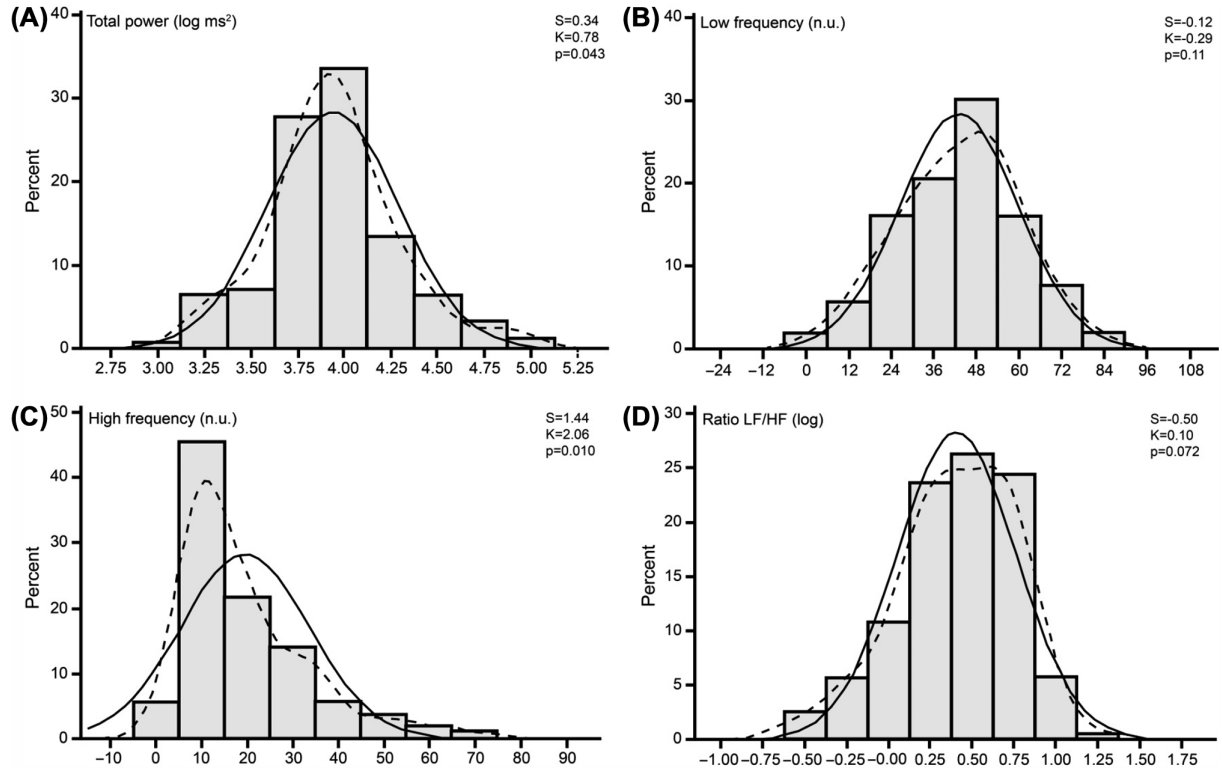
Supplementary Table II. Changes in heart rate and heart rate variability by type of analysis and randomization group.

	Type of analysis							
	All patients				Cohort			
Characteristic Randomization	Old	New	Δ (CI)	*p*	Old	New	Δ (CI)	*p*
Number	72	84			39	47		
Heart rate (beats/min)	−9.5 ± 1.6‡	−2.2 ± 1.4	7.3 (5.6 to 9.4)	< 0.0001	−10.1 ± 1.8‡	−2.4 ± 1.9	7.3 (4.4 to 10.0)	< 0.0001
Total power (log ms^2)	−0.16 ± 0.05†	−0.04 ± 0.06	0.14 (0.05 to 0.23)	0.0029	−0.11 ± 0.07	−0.01 ± 0.06	0.07 (−0.04 to 0.18)	0.22
(Percent)	−5.1	−1.0	4.1 (1.5 to 6.7)		−2.8	−0.25	2.5 (−1.4 to 6.5)	
Low-frequency power (nu)	−2.6 ± 2.6	−0.44 ± 2.1	3.5 (0.02 to 6.9)	0.050	−3.3 ± 3.5	−3.2 ± 2.6	3.7 (−0.63 to 8.0)	0.09
High-frequency power (nu)	6.2 ± 2.2†	2.3 ± 1.9	−2.7 (−5.7 to 0.35)	0.085	4.6 ± 3.2	3.0 ± 2.5	−2.3 (−6.3 to 1.8)	0.28
Low- to high-frequency ratio	−0.16 ± 0.06†	−0.06 ± 0.05	0.09 (0.02 to 0.16)	0.020	−0.15 ± 0.08	−0.10 ± 0.06	0.08 (−0.01 to 0.18)	0.097
(Percent)	−38.1	−14.5	23.6 (3.9 to 42.0)		−36.6	−22.2	14.4 (−2.4 to 31.2)	

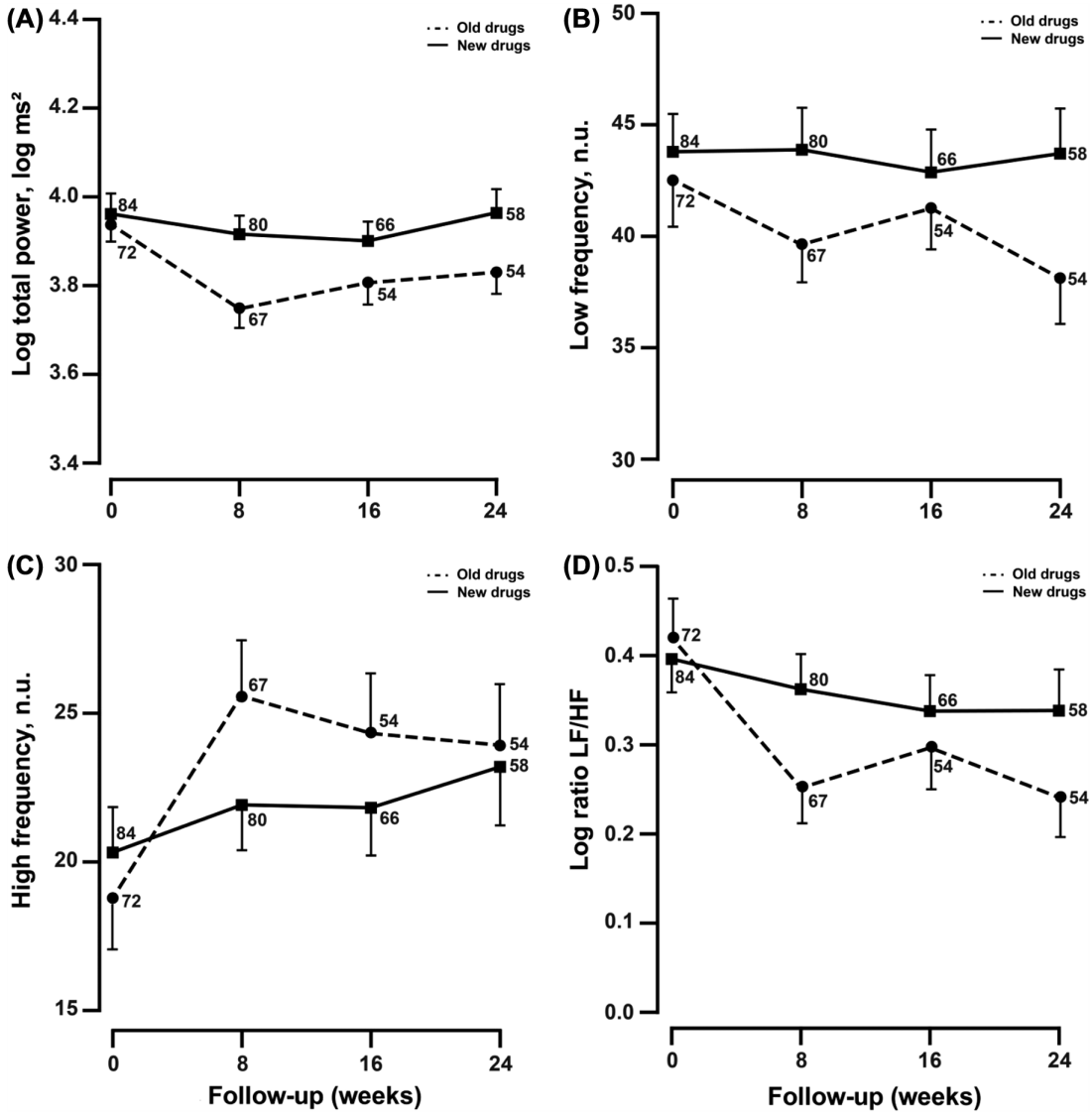
The overall analysis encompasses patients with at least one measurement of heart rate variability after randomization and the cohort analysis patients with all scheduled visits available for analysis. Heart rate variability was analyzed using autoregressive modelling. Within-group changes (follow-up minus baseline) are mean± SE. Δ (CI) refers to the baseline-adjusted differences 95% confidence interval) of the treatment effects (new minus old). *p*-values were computed using a mixed model. Significance of the within-group changes $^*p \leq 0.05$; $^\dagger p \leq 0.01$; $^\ddagger p \leq 0.001$.



Supplementary Figure 1. Frequency distributions of total (A), low-frequency (B) and high-frequency (C) power and the low-to-high-frequency ratio (D) at randomization, based on the fast Fourier transform. *S* and *K* are the coefficients of skewness and kurtosis. The *p*-value is for departure of the actually observed distribution (Kernel distribution; dotted line) from normality (full line).



Supplementary Figure 2. Frequency distributions of total (A), low-frequency (B) and high-frequency (C) power and the low-to-high-frequency ratio (D) at randomization, based on the autoregressive modelling. *S* and *K* are the coefficients of skewness and kurtosis. The *p*-value is for departure of the actually observed distribution (Kernel distribution; dotted line) from normality (full line).



Supplementary Figure 3. Total (A), low-frequency (B) and high-frequency (C) power and the low-to-high-frequency ratio (D) at randomization and during follow-up in patients randomized to old drugs ($n = 72$) or new drugs ($n = 84$). Heart rate variability was analyzed using autoregressive modelling. Plotted values are mean ± SE. The number of patients contributing to the means is given. p-values denote the significance of the between-group differences derived from a mixed model. Significance of the between-group differences at individual visits: $^{*}p \leq 0.05$; $^{\dagger}p \leq 0.01$; $^{\ddagger}p \leq 0.001$.