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Effects of Initiating Antihypertensive Therapy with Amlodipine or Hydrochlorothiazide on Creatinine Clearance in Hypertensive Nigerians with Type 2 Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration between all authors. Authors GBSI and EKIO designed the study, wrote the protocol and the first draft of the manuscript. Authors OOBI and SII searched references for the paper, performed the statistical analysis and managed the analysis of the study. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: To assess the effects of initiating antihypertensive therapy with amlodipine (AML) or hydrochlorothiazide (HCZ) for 48 weeks on creatinine clearance (Clcr) in hypertensive Nigerians with type 2 diabetes mellitus (DM).
Study Design: Randomized, open-label, prospective, outpatient study.
Place and Duration of Study: Department of Pharmacology and Therapeutics, College of Medicine, Ambrose Alli University, Ekpoma, Edo State, Nigeria between March 2008 and March 2009.
Methodology: We randomized 40 newly diagnosed hypertensive subjects with controlled

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type 2 diabetes mellitus (DM) aged 43-68 years to AML and HCZ treatment groups of 20 patients each (20 males (M) and 20 females (F)) and they were treated monotherapeutically, respectively, with AML 10mg and HCZ 25mg, all given once daily for 48 weeks. Body mass index (BMI), blood pressure (BP), 24h urine volume, urine creatinine, serum creatinine and the corresponding Clcr for each day were evaluated at baseline before treatment and at the end of weeks 1, 3, 6, 12, 24, 36 and 48 during treatment.

Results: The 2 drugs significantly reduced BP and at week 48, the mean M vs F systolic BP (SBP)/Diastolic BP (DBP) decrease from baseline for AML group *(27.0/17.5 vs 29.5/20.0 mmHg)* was more significant than that of HCZ group *(23.5/17.5 vs 22.0/16.5 mmHg, P < .01).* HCZ caused maximum M vs F diuresis *(1593.00 +/- 27.21 vs 1587.00 +/- 30.60 ml)* at week 3 and this was significantly higher than that *(1526.00 +/- 27.10 vs 1516.00 +/- 22.76 ml, P < .01)* produced by AML. Although the treatment effect exerted by the 2 drugs on Clcr was significant (*P* =.05), time-dependent changes in the mean values, which were higher in AML group, were not significantly different.

Conclusion: It is demonstrated that in hypertensive Nigerians with type 2 DM, single daily doses of these medications do not have a clinically significant effect on Clcr over a long-term monotherapy. Accordingly, with regard to HCZ greater diuresis which may cause problems particularly in the elderly, AML appears to be a preferred logical alternative to substitute for low dose HCZ therapy.

Keywords: Amlodipine and hydrochlorothiazide; antihypertensive therapy; creatinine clearance; type 2 diabetes mellitus; Nigerians.

1. INTRODUCTION

Hypertension and type 2 DM are worrisome public health concerns worldwide because epidemiologic studies identify each of them as independent predictors of renal insufficiency [1-2]. In addition, regardless of the association between hypertension and DM, when the two coexist, high BP is associated with rapid progression; and adequate treatment of hypertension prevents or slows progression of renal disease and reduces the risk of end stage renal disease (ESRD) [3-5]. Therefore, there is great interest or concern in the choice of a drug or drugs to initiate antihypertensive therapy in these high risk patients as this has important implications on renal outcomes [6-7].

In diabetic and non-diabetic hypertensive patients without or with established renal insufficiency and proteinuria, drugs that inhibit the renin angiotensin aldosterone system (RAAS) have been suggested to be superior to other conventional therapy in preventing or slowing decline in renal function [3-5,8-10]. But it is well documented that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin 2 AT_1 receptor blockers (ARBs) are less effective in hypertensive blacks compared to whites when used as monotherapy unless combined with diuretics or calcium channel blockers (CCBs) [11-14]. Accordingly, diuretics or CCBs have been suggested as obvious first choice agents [12,15,16]. However, there are very few studies in Nigeria that have compared the efficacy of diuretics and CCBs on renal function in hypertensive type 2 diabetic patients with normal renal function.

The glomerular filteration rate (GFR) is a direct measure of renal function. As it is not easy to measure the GFR directly, the serum creatinine concentration is used to access renal function. However, Clcr provides a more accurate assessment from the results of a 24h

urine collection [17]. It has been reported that diuretics, such as HCZ, by reducing plasma volume and decreasing renal perfusion can cause a fall in GFR resulting in prerenal azotaemia, a reversible form of chronic kidney disease (CKD) [18].

There are also clinical data that demonstrate that some dihydropyridine CCBs (DCCBs) such as AML, by their peculiar effects on renal haemodynamics, may not offer renoprotection unless co-administered with ACEI or ARB [15-16, 19]. The majority of studies in blacks vis-à-vis renal disease in the context of DM and hypertension have been done in Africans in diaspora but not in native blacks born and living in Africa, nay in Nigeria. In fact, it has been reported that native blacks of sub-Saharan African descent differ from white persons and other populations in sociocultural, psychological and biological characteristics [20-21]. Consequently, we have studied the effects of initiating antihypertensive therapy with AML or HCZ on Clcr in hypertensive Nigerians with type 2 DM born and living in Nigeria.

2. MATERIALS AND METHODS

2.1 Study Population

We enrolled into the study 40 type 2 diabetic Nigerians of both gender with newly diagnosed essential hypertension (stages 1 and 2) aged 43-68 years and who were attending Central Hospital and Osigbemhe Hospital both in Auchi in Edo State of Nigeria between March 2008 and March 2009. The sample size was estimated based on the number of Nigerians that are believed to have hypertension with concomitant type 2 DM [22]; and to detect a difference of 2 units in mean change in the measured variables, between both treatment arms with a power equal to 90% using a one sample t-test at a one-sided significance level of .05, this requires 20 patients per group. Eligible participants had qualifying hypertension of BP > 160/90 and ≤180/120 mmHg measured on at least 2 occasions in lying/supine, sitting and standing positions using standardized methods [23]. Excluded were patients with identifiable cause of the hypertension except type 2 DM, clinical evidence of cerebrovascular, cardiac, renal, hepatic, gastrointestinal or endocrinologic disease except type 2 DM, hypersensitivity to AML and HCZ or related drugs, history of smoking, alcohol intake, substance abuse or mental illness. Also excluded were patients needing any concomitant medication (apart from oral antidiabetic drugs) eg digitalis, non-steroidal anti-inflammatory drugs, psychotropic drugs, monoamine oxidase inhibitors or oral contraceptives, that may interact with the trial drugs and pregnant or lactating females.

Controls comprised the parallel age and sex-matched hypertensives on HCZ. The research protocol was reviewed and approved by the Ethics Committees of Irrua Specialist Teaching Hospital Irrua, Nigeria (Ambrose Alli University College of Medicine Teaching Hospital) and Central Hospital Auchi, Nigeria. After suitable explanation of the study protocol in lay language, all literate patients gave informed written consent and the illiterates thumb-printed the consent form before the beginning of the study.

2.2 Study Design

Subjects were examined by a standardized pre-tested questionnaire seeking information on demographic data, the history of hypertension, DM, current drugs if any, educational and social status, dietary habits, smoking and alcohol intake, etc. The 40 patients were randomized to AML and HCZ groups each comprising 20 patients (10 males (M) + 10 females (F)) using computer program-generated random numbers. Diabetes was treated in

32 patients with oral hypoglycaemic agents viz a sulfonylurea (glibenclamide 5 mg once daily) and a biguanide (metformin 500 mg once or twice daily) and in 8 patients with gliclazide 80 mg once or twice daily. Patients were instructed to take medications between 8 am and 10 am every morning.

2.3 Measurements of Heights (m), Weights (wt) (kg) and BP (mmHg)

A stadiometer scale (Seca model, UK) was used for measuring height, with no shoes on; and a beam balance (Hackman, UK) was used to measure wt while on light clothing. BMI was computed as wt divided by height squared. SBP and DBP were measured with a standard mercury sphygmomanometer (Riester Diplomat Presameter, Germany) using standardized methods [23] at the sitting, standing and supine positions; always between 8am and 10am. All constricting clothing on the upper arm was removed before any measurement and subjects were discouraged from talking or moving during measurements. The first phase of the Korotkov sound was regarded as the SBP while the fifth phase was regarded as the DBP. During measurement, readings were taken two consecutive times with an interval of at least one minute and the average recorded. During the study, subjects were not told the results of BP measurement.

2.4 Antihypertensive Intervention

Patients in AML group were treated initially with AML 5 mg and the dose was doubled after 6 weeks if BP was not controlled while in HCZ group patients were treated with HCZ 25 mg, both medications being administered once daily. The outpatient treatment lasted 48 weeks. The patients were monitored closely and outcome measures evaluated at baseline before treatment and at the end of weeks 1, 3, 6, 12, 24, 36 and 48 during treatment. Unequivocal patient identification was possible via a patient identification list consisting of the patient number, first name and surname.

The study medications AML and HCZ are licensed for long-term treatment of hypertension so that dangerous side effects due to the medicaments were not to be expected. AML 5mg and 10mg tablets (Amlovar^{R}), were donated by Neimeth International Pharmaceuticals Ikeja, Nigeria: NAFDAC Reg No A4-0333; Manufacturing Date 07-2007 and Expiry Date 07-2010. HCZ 25mg tablets (Esidrex^{R}) were donated by Novartis Pharma SAS Nigerian Representative, NAFDAC Reg No OL-3705, Manufacturing Date 08-2007 and Expiry Date 08-2010.

2.5 Course of Study and Methods for Recording Efficacy and Safety

All patients were advised to maintain their usual diet (weight-maintaining no-salt-added diet) and regular physical activity but to avoid undue stress throughout the duration of the study. They were instructed to take their drugs every morning. Each patient was observed for about 2 hours after taking medication drug for the first time. Adherence in respect of intake of medication was encouraged by interviewing patients through phone calls, sporadic visits and pill counts outside the view of patients. To preclude white-coat effect, observer bias and to accurately assess the efficacy of the drugs, patients were followed up repeatedly at weeks 1, 3, 6, 12, 24, 36, and 48. At each visit, volunteered or spontaneous report of adverse events were assessed for severity and association with treatment; and the attending physicians/investigators also recorded any adverse events they observed themselves or

elicited from the patient through careful interrogation like “How do you feel?” No patient withdrew from the study because of adverse events.
Response to therapy as regards BP measurement was defined as a decrease in the mean trough sitting SBP and DBP of 10 mmHg or a drop to < 90 mmHg with reduction of > 5 mmHg. BP was regarded as controlled if the DBP was < 80 mmHg and SBP < 130 mmHg. The effects of treatment on the various variables (except height) were assessed by comparing the values at each visit with the pretreatment baseline values.

2.6 Collection of Samples and Analysis

2.6.1 Urine

Each subject collected a 24h urine sample into a plastic container from Sunday 7am to Monday 7am at baseline (week 0) before treatment and on the evaluation days. The need to carefully collect all urine passed was well emphasized. The urine samples were screened for completeness by examining the sex-specific amount of creatinine in each sample. The volume of 24h urine was measured with a measuring cylinder and recorded. The creatinine concentration was determined using Jaffe’s method [24].

2.6.2 Blood

At baseline and at the end of weeks 1, 3, 6, 12, 24, 36, and 48, 5ml of venous blood was obtained from every patient by peripheral venepuncture into a plain sterile bottle. From the prepared serum sample of each subject, serum creatinine concentration was assayed using Jaffe’s method [24].

2.6.3 Calculation of Clcr

Clcr values corresponding to baseline, weeks 1, 3, 6, 12, 24, 36 and 48 were calculated using the formula:

$$\text{Clcr(ml/min)} = \frac{\text{mg creatinine/dl urine} \times \text{ml urine/24h}}{\text{mg creatinine/dl serum} \times 1440}$$

2.7 Statistical Analysis

All data are presented as mean ± SEM or mean ± SD (for age, height and weight) using the Proc ANOVA of SAS (2004) which tested the changes in variables between baseline and week 48. Where significant differences were noticed, mean separation was carried out using Duncan Multiple Range Test. Correlation between two sets of variables was determined using Spearman’s rank correlation. $P = .05$ was regarded as significant in all cases.

3. RESULTS AND DISCUSSION

As shown in Table 1, the two randomized treatment groups that were divided into 4 subgroups were comparable with respect to the main demographic and clinical characteristics. There were no drop-outs, hospitalization or morbidity related to either hypertension or DM during the period. The effects of trial drugs on BP are presented in Table 2. The duration of treatment effect on SBP and DBP was significant and AML significantly decreased the variables more than HCZ. Mean M vs F decrements from

baseline were 27.0/17.5 vs 29.5/20.0 mmHg for AML group and 23.5/17.5 vs 22.0/16.5 mmHg for HCZ group, respectively.

Table 1. Demographic characteristics and baseline blood pressures of hypertensive diabetic subjects (N = 20 [10M + 10F] per group)

Group	Characteristics	Male		Female	
		Range	Mean±SD/SEM*	Range	Mean±SD/SEM*
AML	Age (yrs)	46-61	53.90±5.04	45-62	53.10±5.38
	Height (m)	1.59-1.73	1.66±0.04	1.58-1.71	1.64±0.05
	Weight (kg)	74-90	83.20±5.13	72-89	80.0±4.71
	BMI. (kg/m^2)	29.37-30.10	30.25±0.24	28.92-30.48	29.00±0.70
	SBP(mm Hg)	150-180	164.50±3.76*	155-180	166.50±2.24*
	DBP(mm Hg)	100-115	104.50±1.89*	100.110	105.00±1.57*
HCZ	Age (yrs)	45-65	52.40±6.75	43-68	54.50±7.73
	Height (m)	1.62-1.74	1.68±0.04	1.58-1.70	1.64±0.03
	Weight (kg)	77-90	84.51±4.32	63-86	76.44±6.54
	BMI (kg/m^2)	29.39-30.00	29.96±0.19	26.30-29.76	27.50±0.53
	SBP(mm Hg)	98-180	162.50±3.71*	150-180	162.00±2.62*
	DBP(mm Hg)	90-115	104.50±1.89*	100-115	102.50±2.71*

*Characteristics and blood pressures are not significantly different between the groups and hypertensives are relatively younger with high BMIs; AML, Amlodipine; HCZ, Hydrochlorothiazide; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; M, male; F, female; *, Standard error of mean*

Table 2. Effects of monotherapy with AML and HCZ for 48 weeks on BP (mmHg) in type 2 hypertensive diabetic subjects

Week	BP	Treatment subgroups (male)		Treatment subgroups (female)		Gender effect
		AML	HCZ	AML	HCZ	
0	SBP	164.50±3.76	165.00±3.71	166.50±2.24	162.00±3.59	
	DBP	103.60±1.89	104.50±1.89	104.50±1.57	102.50±2.71	
1	SBP	161.50±3.17	162.00±3.51	163.00±2.49	160.00±3.33	
	DBP	100.50±1.17	102.00±2.49	102.00±1.33	100.00±2.69	
3	SBP	$158.50\pm3.58_A$	$157.50\pm3.75_A$	$161.50\pm1.98_A$	$156.50\pm2.48_A$	
	DBP	$99.00\pm0.69_A$	$97.50\pm2.01_A$	$98.00\pm1.33_A$	$98.00\pm2.49_A$	
6	SBP	$151.50\pm2.99_B$	$152.50\pm2.81_B$	$156.00\pm2.21_B$	$151.00\pm3.15_B$	
	DBP	$90.00\pm2.11_B$	$94.00\pm1.63_A$	$93.00\pm1.50_B$	$92.00\pm1.53_B$	
12	SBP	$146.50\pm2.36_C$	$148.50\pm2.99_C$	$152.00\pm1.70_B$	$146.50\pm2.79_C$	$\underline{0.320}^{NS}$
	DBP	$87.50\pm1.54_C$	$87.50\pm1.17_B$	$90.50\pm1.17_B$	$88.00\pm1.53_C$	0.877^{NS}
24	SBP	$142.50\pm2.14_C$	$146.50\pm3.34_C$	$145.00\pm2.17_C$	$145.00\pm3.07_C$	
	DBP	$86.50\pm1.50_B$	$87.00\pm1.34_B$	$89.50\pm0.50_C$	$87.50\pm1.71_C$	
36	SBP	$142.00\pm2.00_C$	$143.00\pm3.59_D$	$141.00\pm1.94_D$	$142.00\pm3.82_D$	
	DBP	$86.00\pm1.63_C$	$87.00\pm1.53_B$	$88.00\pm1.33_C$	$86.00\pm1.80_C$	
48	SBP	$137.50\pm2.61_D$	$141.50\pm3.42_D$	$137.00\pm2.26_D$	$140.00\pm3.58_D$	
	DBP	$86.00\pm1.63_C$	$87.00\pm1.53_B$	$84.50\pm1.57_D$	$86.00\pm1.80_C$	

Significant differences within columns are indicated by ABCD (P = .05): There are significant time-dependent reductions in BP in groups; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; AML, amlodipine; HCZ, hydrochlorothiazide; NS, not significant; (N = 10 per subgroup)

Table 3 shows that the time dependent effect on 24h urine volume was significant (P<.001), for diuresis was significant in M and F HCZ subgroups at week 3 and in AML subgroups at week 12. Although the treatment effect on Clcr was significant (P<0.05), the changes in mean values over time were not significant. Mean values were higher in AML group (Table 4).

Table 3. Effects of monotherapy with AML and HCZ on 24h urine volume (ml) in type 2 diabetic hypertensive subjects for 48 weeks

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	1483.00±27.21	1472.00±33.56	1460.00±22.31	1489.00±26.10	
1	1501.00±27.67	1565.00±36.06	1485.00±21.92[b]	1567.00±30.55[a]	
3	1526.00±27.10	1593.00±27.21$_A$	1516.00±22.76	1587.00±30.60$_A$	
6	1536.00±26.41	1520.00±28.40	1530.00±22.80	1536.00±27.01	
12	1538.00±26.05$_A$	1498.00±32.28	1534.00±21.09$_A$	1517.00±25.12	0.898^{NS}
24	1525.00±25.70	1492.00±32.52	1516.00±22.57	1506.00±25.48	
36	1506.00±27.86	1487.00±33.67	1488.00±22.99	1504.00±25.43	
48	1504.00±28.10	1483.00±33.13	1466.00±22.12	1498.00±27.28	

Significant differences within columns are indicated by AA and within rows by ab (P = .05): There is significant time-dependent diuresis at week 12 in AML subgroups and at week 3 in HCZ subgroups; other abbreviations are as used in Table 2; (N=10 per subgroup).

Table 4. Effects of monotherapy with AML and HCZ on creatinine clearance (ml/min) in type 2 diabetic hypertensive subjects for 48 weeks

Week	Treatment subgroups (Male)		Treatment subgroups (Female)		Gender effect
	AML	HCZ	AML	HCZ	
0	113.40±3.02	111.20±3.39	106.50±2.61	105.90±3.26	
1	113.90±2.96	116.90±3.35	108.30±2.66	111.30±3.36	
3	115.20±2.92	113.80±3.50	110.80±2.76	107.30±3.63	
6	117.50±2.96	114.00±3.45	113.40±3.06[a]	109.50±3.53[b]	
12	117.20±3.16[a]	112.10±3.45[b]	113.90±3.01[a]	108.00±3.43[b]	0.795^{NS}
24	116.50±3.05[a]	111.20±3.42[b]	112.50±2.90[a]	107.40±3.37[b]	
36	114.00±3.16[a]	110.90±3.39[b]	109.50±2.98	106.90±3.37	
48	114.90±3.06[a]	110.50±3.38[b]	107.70±2.77	105.70±3.35	

Significant differences within rows are indicated by ab (P = .05): Significant treatment effects are demonstrated and there are time-dependent changes in mean values which are higher in males culminating in moderate increase (AML subgroups) and decrease (HCZ subgroups); other abbreviations are as used in Table 2; (N =10 per subgroup)

Despite lowering of BP, initiating therapy with AML or HCZ for 48 weeks did not appear to have a significant effect on renal haemodynamics as observed from the Clcr. However, Clcr levels were higher in M than F. The above finding confirms previous reports by Lam et al. [25], Tuomilehto et al. [26], Okoro and Oyejola [27]. Also, according to Rahman et al. [28], there was no significant difference over time in diabetics and nondiabetics between chlorthalidone, AML or lisinopril treatment in preventing a 50% or a greater decrement in GFR as well as reducing the development of ESRD. Thus, the results of the current study confirm the report of Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

In the present study, most of the subjects were older than 58 years. Major age-related physiologic changes that influence drug prescribing are the progressive losses after maturity in individual organs, especially the kidneys. The most important physiologic change, in terms of drug therapy, is the alteration in kidney function which is accompanied by a reduced capacity of the elderly to dispose of drugs eliminated in the urine [25]. According to Rowe [29], normal elderly individuals have GFRs significantly less than those of young individuals. The clinical impact of this decrease is augmented by the lack of change in serum creatinine concentration despite the decrease in renal function. Although, serum creatinine is generally used as a guide to renal function because it is easier to obtain than a 24h Clcr, it is often inaccurate and leads to treatment errors, particularly in the elderly in whom it overestimates renal function because creatinine is produced in the muscle, and muscle mass decreases with age [29]. Here lies the importance of this study which demonstrates for the first time, to our knowledge, that these drugs do not have deleterious effects on the kidneys in hypertensive Nigerians with type 2 DM during 48 week treatment duration.

In the current study, even though the effects of AML or HCZ on Clcr were not deleterious during the treatment period, the question of nephrotoxicity of long-term thiazide therapy continues to surface [30-33]. Recently, Reungjul et al. [32] reported that rats that received thiazides chronically showed evidence of "subtle glomerular injury characterized by periglomerular fibrosis as well as wrinkling and thickening of the glomerular basement membrane". The kidney showed evidence of oxidative stress as well, and the adverse effects were not mimicked by diet-induced potassium deficiency. The authors therefore speculate that the changes might have resulted from glomerular ischaemia. Hence, they suggest that diuretic treatment of humans may damage the kidney and "may not be necessary in many patients", particularly those with chronic kidney disease and diabetics.

Although the structural and functional changes in rat kidney reported are impressive, it may be best to be circumspect before imputing similar changes to human use as effects may differ between species [34]. Overall, there is little evidence that thiazide diuretics when taken by humans chronically at low or moderate doses, increase the risk for chronic kidney disease or structural renal damage. Nevertheless, thiazides are known to reduce GFRs functionally; in rats thiazides reduce GFRs by activating tubuloglomerular feedback [35]. In the ALLHAT Collaborative Research Group [36], an analysis of individuals with baseline estimated GFRs < 60 ml/min per 1.73m^2 found that the GFR after 6 years of treatment was lower with a thiazide diuretic than with AML [28]. In the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) Trial [37], HCZ was less renoprotective compared to AML. In the Intervention as a Goal in Hypertension Treatment (INSIGHT) Trial [38], nifedipine GITS seemed to be more renoprotective compared with HCZ-amiloride by having a greater preventive effect on the decline in estimated GFR and subsequent progression to renal insufficiency. A post-hoc analysis of the Systolic Hypertension in Europe (Syst-EUR) Trial [39] showed that HCZ significantly increased serum creatinine from baseline ($P < .001$) whereas a DCCB nitrendipine did not. However, it has been reported that thiazides reduce proteinuria in hypertensive patients treated with drugs that block the RAAS [40]. Thus, the current opinion is that a small decline in GFR may not necessary imply renal toxicity [41].

4. CONCLUSION

This study demonstrates that AML and low dose HCZ are safe in the treatment of Nigerians with essential hypertension and type 2 DM, and who have normal renal function, during a long-term monotherapy. In addition, with regard to HCZ greater diuresis and other problems

which may be more serious in the elderly and diabetics, AML appears to be a preferred logical alternative to substitute for low dose HCZ therapy. Since the characteristic age-related decline in renal function may affect drug response as well as drug disposition, Clcr measurement remains an important tool to prevent drug toxicity particularly in the elderly. All the same, it must be emphasized that caution should be exercised in making deductions from our findings or extrapolating our data to hypertensive black type 2 diabetic patients in general because of the small number of patients studied. Further research with larger sample sizes is necessary.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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