

# Gender difference in the response to an angiotensin-converting enzyme inhibitor and a diuretic in hypertensive patients of African descent

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**Background** The efficacy of angiotensin-converting enzyme (ACE) inhibitors in decreasing blood pressure in African patients is controversial.

**Objective** We examined the ambulatory blood pressure (ABP) response to a diuretic and an ACE inhibitor in hypertensive patients of East African descent and evaluated the individual characteristics that determined treatment efficacy.

**Design** A single-blind randomized AB/BA crossover design.

**Setting** Hypertensive families of East African descent from the general population in the Seychelles.

**Participants** Fifty-two (29 men and 23 women) out of 62 eligible hypertensive patients were included.

**Main outcome measures** ABP response to 20 mg lisinopril (LIS) daily and 25 mg hydrochlorothiazide (HCT) daily given for a 4-week period.

**Results** The daytime systolic/diastolic ABP response to HCT was 4.9 [95% confidence interval (CI) 1.2–8.6]/3.6 (1.0–6.2) mmHg for men and 12.9 (9.2–16.6)/6.3 (3.7–8.8) mmHg for women. With LIS the response was 18.8 (15.0–22.5)/14.6 (12.0–17.1) mmHg for men and 12.4 (8.7–16.2)/7.7 (5.1–10.2) mmHg for women. The night-

time systolic/diastolic response to HCT was 5.0 (0.6–9.4)/2.7 [(-0.4)–5.7] mmHg for men and 11.5 (7.1–16.0)/5.7 (2.6–8.8) mmHg for women, and to LIS was 18.7 (14.2–22.1)/15.4 (12.4–18.5) mmHg for men and 3.5 [(-1.0)–7.9]/2.3 [(-0.8)–5.4] mmHg for women. Linear regression analyses showed that gender is an independent predictor of the ABP responses to HCT and to LIS.

**Conclusions** Hypertensive patients of African descent responded better to LIS than to HCT. Men responded better to LIS than to HCT and women responded similarly to both drugs. *J Hypertens* 22:1213–1220 © 2004 Lippincott Williams & Wilkins.

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**Keywords:** diuretics, angiotensin-converting enzyme inhibitors, crossover design, hypertension, gender, Africa

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## Introduction

It has been reported that blood pressure is lowered less with angiotensin-converting enzyme (ACE) inhibitors than with diuretics in individuals of African descent [1–4]. However, situations that stimulate the renin-angiotensin system, such as taking a diuretic or having a low dietary salt intake, can restore a good response to blockade of the renin-angiotensin system in African-Americans [3,5] and in Africans [6–8]. Likewise, maintaining a low salt intake can diminish the race-related difference in drug response [9].

In this study we examined the ambulatory blood pressure (ABP) responses to a diuretic and to an ACE inhibitor in hypertensive patients of African descent using a randomized single-blind crossover design. In

view of the known variability in the individual response to antihypertensive drugs [10–13], we also examined individual characteristics that determine treatment efficacy.

## Methods and subjects

The study took place in the Seychelles islands, which are populated predominantly by individuals of East African descent. Two previous population surveys showed a high prevalence of hypertension in the adult population [14,15].

Participants in this study were recruited from a family-based study of genetic determinants of hypertension conducted between August 1999 and January 2002. For this genetic study, families with several hypertensive

patients were selected on the basis of a national hypertension register. Participants in this study were individuals who had a daytime ABP > 140/90 mmHg after a 2-week washout period during which antihypertensive medications, if any, were stopped. Patients were excluded if they presented a contraindication to one of the study drugs (e.g. gout, known previous allergic reaction), systolic/diastolic blood pressure > 200/120 mmHg, renal failure, insulin-dependent diabetes mellitus or a history of cardiovascular event during the previous 6 months. Pre-menopausal women were included only if they had undergone sterilization or were taking a contraceptive treatment. After the 2-week washout period and prior to starting the drug treatments, participants were requested to collect urine during 24 h under their usual diet. The study was approved by the Ministry of Health of Seychelles and the ethical committee of the University of Lausanne (Switzerland). All participants were informed of the nature of the study and gave a written informed consent.

A single-blind AB/BA crossover design was used. After the washout period, the participants were randomly allocated, using a block randomization scheme by group, to receive a 4-week course of hydrochlorothiazide (HCT) (25 mg once daily) followed by another 2-week washout and a 4-week course of lisinopril (LIS) (20 mg once daily) for Group 1 or the inverse sequence for Group 2.

ABP monitoring was performed at the start and at the end of each treatment period (on the day preceding the initiation of the medication and on the day preceding the cessation of the medication). This investigation was conducted using Diasys devices (DIASYS Integra; Novacor SA, Rueil-Malmaison, France) placed on the left arm with an appropriately sized cuff. Measurements were based on the auscultatory mode relayed by the oscillometric mode in case of failure of the auscultatory mode. Blood pressure was recorded every 20 min during the day and every 30 min during the night. Daytime ABP in this study is the average of all validated BP readings between 0700 h and patients' self-reported bedtime (which ranged between 1930 and 0100 h, median: 2200 h). Night-time ABP is the average of all validated BP readings between the patients' self-reported bedtime and 0700 h the next morning. We excluded observations for the following reasons: systolic blood pressure (SBP) < 50 mmHg or > 250 mmHg; diastolic blood pressure (DBP) < 30 mmHg or > 150 mmHg; differential blood pressure (SBP-DBP) < 10 mmHg or > 150 mmHg; and pulse < 35 beats/min or > 250 beats/min. All participants had at least 29 valid measurements and 90% at least 40 for each ABP monitoring. The average ( $\pm$  SE) number of valid measurements was 37 ( $\pm$  1) for daytime and 15 ( $\pm$  1) for

night-time ABP for HCT, and 38 ( $\pm$  1) and 15 ( $\pm$  1), respectively, for LIS.

A subgroup of participants ( $n = 33$ ), allocated according to device availability (10 devices were available), received their pills in electronic medication bottles (medication event monitoring systems, MEMS; Aardex, Zug, Switzerland). Electronic monitoring is considered to be the best available approach to monitoring compliance and has been used in several studies [16,17], including one in the Seychelles [18]. Good compliance was arbitrarily defined as having more than 90% of days with at least one opening of the bottle. There was no difference in gender, age, treatment group and initial blood pressure between participants who received a MEMS device and those who did not.

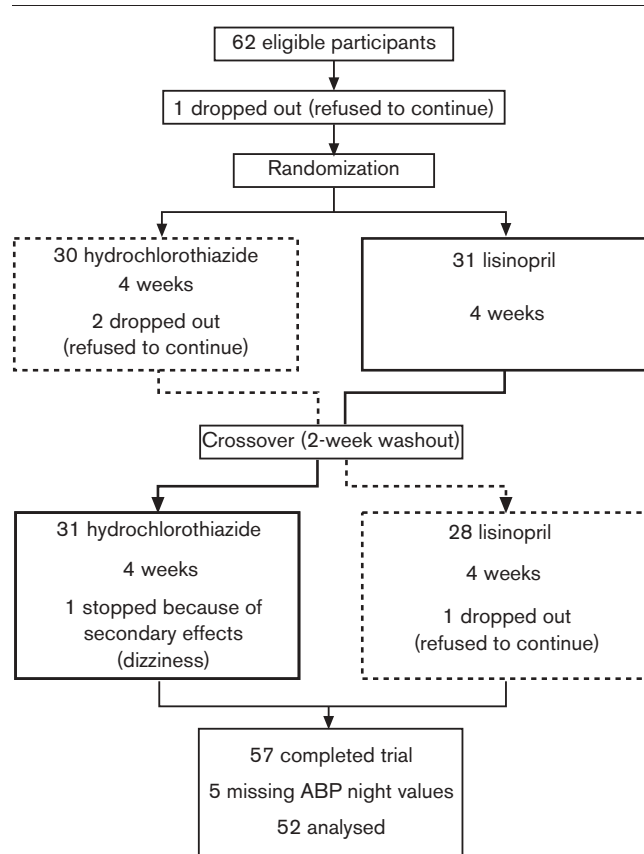
### Statistical analysis

We needed 32 participants to detect a difference of 5 mmHg (with a standard deviation of 10 mmHg) between the two treatments with an 80% power and a 5% type 1 error. The response to treatment was estimated by the difference in systolic/diastolic/mean ABP between the start (baseline) and the end of the 4-week treatment periods. The mean arterial blood pressure (MAP) was calculated as 2/3 of the diastolic + 1/3 of the systolic blood pressure. Descriptive statistics were conducted using two-sample *t*-tests for continuous variables and chi-square tests for categorical variables. To assess the different treatment contrasts, we conducted repeated measures ANOVA, followed by *t*-tests whenever the global ANOVA *F* test was significant. We used a Bonferroni procedure to account for multiple comparisons. Among the contrasts evaluated, we compared baseline blood pressure values between groups to assess any carry-over effect. The relationship between the MAP response (used as the dependent variable under either LIS or HCT) and selected factors [i.e. age, gender, body mass index (BMI) and urinary sodium excretion] was examined with univariate and multivariate linear regression analyses, which included an assessment of interaction terms. We checked for any violation of the assumptions underlying linear regression. Gender-specific and age-adjusted ABP responses were also calculated using linear regression. Analyses were done using Stata 7.0 (Stata Corporation, College Station, Texas, USA). Corrected *P* values < 0.05 were considered statistically significant.

### Results

Sixty-one of the 62 eligible patients agreed to participate. Among the 61 participants, 57 completed the study (93.4%) and four dropped out [three refused to continue and one had side-effects (dizziness while under HCT treatment)], and, of these 57, five had missing values for night ABP, leaving 52 individuals for analysis (Fig. 1). Baseline participants' characteristics

Fig. 1



Study design and inclusion of patients.

are shown in Table 1. Men had higher baseline diastolic ABP pressure than women. Baseline daytime and night-time ABP did not differ between groups (HCT–LIS sequence versus LIS–HCT sequence). The mean ( $\pm$  SE) 24-h urinary sodium excretion before treatment was  $99 \pm 10$  mmol/24 h for men and  $108 \pm 13$  mmol/24 h for women or, equivalently, respectively  $5.4 \pm 0.6$  and  $5.9 \pm 0.7$  g of sodium chloride/day, which suggests a moderate average dietary salt intake.

There was no significant carry-over effect, suggesting that the effect of each medication did not depend on the sequence (HCT–LIS or LIS–HCT) along which the medications were given. The global ANOVA results were significant for systolic and diastolic, for daytime as well as for night-time ABP ( $F$  tests,  $P < 0.0001$ ). Both LIS and HCT significantly reduced daytime ( $P < 0.001$ , for systolic and diastolic) and night-time ( $P < 0.005$ , for systolic and diastolic) ambulatory blood pressure (Fig. 2). Overall, LIS induced a larger daytime ABP response than HCT [systolic: 16.0, 95% confidence interval (CI) 12.5–19.4 and 8.4 (5.0–11.9), respectively; and diastolic: 11.5 (9.1–13.9) and 4.8 (2.3–7.2), respectively] (Fig. 2). Results were similar for the

night-time response. In univariate linear regression analyses, older participants responded better to HCT than younger ones ( $P = 0.03$ ) and the opposite trend, although not significant, was seen for LIS ( $P = 0.58$ ). The significance of this effect disappeared when controlling for gender, BMI and urinary sodium excretion in the multivariate regression analysis.

Men showed a greater systolic/diastolic ABP response to LIS than women, and women a greater response to HCT than men (Fig. 3). This was true for the daytime [men, LIS: 18.8 (15.0–22.5)/14.6 (12.0–17.1), HCT: 4.9 (1.2–8.6)/3.6 (1.0–6.2) and women, LIS: 12.4 (8.7–16.2)/7.7 (5.1–10.2), HCT: 12.9 (9.2–16.6)/6.3 (3.7–8.8)] and for the night-time [men, LIS: 18.7 (14.2–22.1)/15.4 (12.4–18.5), HCT: 5.0 (0.6–9.4)/2.7 (–0.4)–5.7) and women, LIS: 3.5 (–1.0)–7.9)/2.3 (–0.8)–5.4), HCT: 11.5(7.1–16.0)/5.7(2.6–8.8)] responses. Men responded better to LIS than to HCT ( $P < 0.001$ , for systolic and diastolic daytime ABP), whereas the response to both antihypertensive drugs was comparable in women ( $P > 0.4$ , for systolic and diastolic daytime ABP) (Fig. 3). The same patterns were observed for night-time SBP and DBP. The age-adjusted systolic/diastolic ABP responses (mmHg) to HCT were 4.9/3.6 during daytime and 5.0/2.7 during night-time for men and 14.5/7.4 and 11.4/6.0, respectively, for women. The age-adjusted systolic/diastolic ABP responses (in mmHg) to LIS were 18.8/14.6 during daytime and 18.7/15.4 during night-time for men, and 12.7/7.0 and 4.0/1.7, respectively, for women.

The overall average compliance was similar for both medications ( $85.5 \pm 3.4\%$  under HCT versus  $90.2 \pm 2.7\%$  under LIS,  $P = 0.23$ ). The compliance did not differ between men and women under LIS (men:  $90.7 \pm 2.4\%$  and women:  $89.5 \pm 5.2\%$ ;  $P = 0.83$ ). Men were slightly, although not significantly, less compliant than women under HCT ( $80.7 \pm 6.0$  versus  $90.7 \pm 2.4\%$ , respectively;  $P = 0.07$ ). Similar gender differences regarding the response to both drugs were observed when conducting a separate analysis for the subgroup of participants who received a MEMS device to monitor their compliance and those with a good compliance. Seventeen men and 16 women were monitored with a MEMS. Among participants with a compliance  $> 90\%$ , the mean systolic/diastolic ABP response (in mmHg) to HCT was 5.5/4.4 (daytime) and 7.2/5.0 (night-time) for men, whereas it was 12.9/5.5 (daytime) and 12.6/7.4 (night-time) for women. Among those with a compliance  $> 90\%$ , the mean systolic/diastolic ABP response (in mmHg) to LIS was 18.9/13.3 (daytime) and 19.8/13.8 (night-time) for men, whereas it was 11.5/7.8 (daytime) and 6.2/3.4 (night-time) for women.

Linear regression analyses indicated that gender was an

Table 1 Participants' characteristics by gender

Parameters	Men (n = 29)		Women (N = 23)		P value
	Mean	(95% CI)	Mean	(95% CI)	
Age (years)	46	(43–50)	52	(48–56)	0.04
BMI (kg/m <sup>2</sup> )	25.9	(24.7–27.1)	26.7	(24.8–28.6)	0.47
Plasma					
Na (mmol/l)	140	(139–141)	140	(138–141)	0.98
K (mmol/l)	3.9	(3.8–4.0)	3.5	(3.4–3.6)	<0.0001
Fasting blood glucose (mmol/l)	5.1	(4.5–5.7)	4.2	(3.8–4.6)	0.02
Cholesterol (mmol/l)	5.6	(5.2–6.1)	5.7	(5.2–6.2)	0.95
HDL-cholesterol (mmol/l)	1.33	(1.17–1.49)	1.35	(1.21–1.49)	0.83
Creatinine (μmol/l)	79	(71–88)	75	(70–80)	0.40
Urine					
Na (mmol/24 h)	99	(78–121)	108	(80–135)	0.61
K (mmol/24 h)	49	(40–58)	41	(35–48)	0.21
Baseline off-treatment ambulatory blood pressures (mmHg)					
Daytime systolic	142	(139–145)	144	(140–148)	0.52
Daytime diastolic	97	(95–100)	92	(89–95)	0.01
Daytime MAP	112	(110–114)	111	(107–112)	0.13
Night-time systolic	126	(122–130)	129	(123–135)	0.42
Night-time diastolic	87	(84–90)	82	(78–86)	0.05
Night-time MAP	100	(97–103)	98	(93–102)	0.35
24-h systolic	138	(135–141)	139	(135–144)	0.62
24-h diastolic	94	(92–97)	89	(86–92)	0.01
24-h MAP	109	(106–111)	106	(103–109)	0.14

BMI, body mass index; HDL, high-density lipoprotein; MAP, mean arterial blood pressure; CI, confidence interval.

independent predictor of the daytime ABP response to HCT and to LIS (Table 2). Results for night-time were similar. When analysing systolic and diastolic blood pressure separately, gender was a better predictor of systolic than of diastolic ABP response to therapy. Again, similar patterns were found for daytime and night-time ABP responses. None of the interaction terms were significant in the multiple linear regression analyses on daytime ABP. In particular, neither age nor group (i.e. HCT–LIS sequence versus LIS–HCT sequence) significantly interacted with gender in the relationship between daytime MAP response and the selected variables with either treatment.

## Discussion

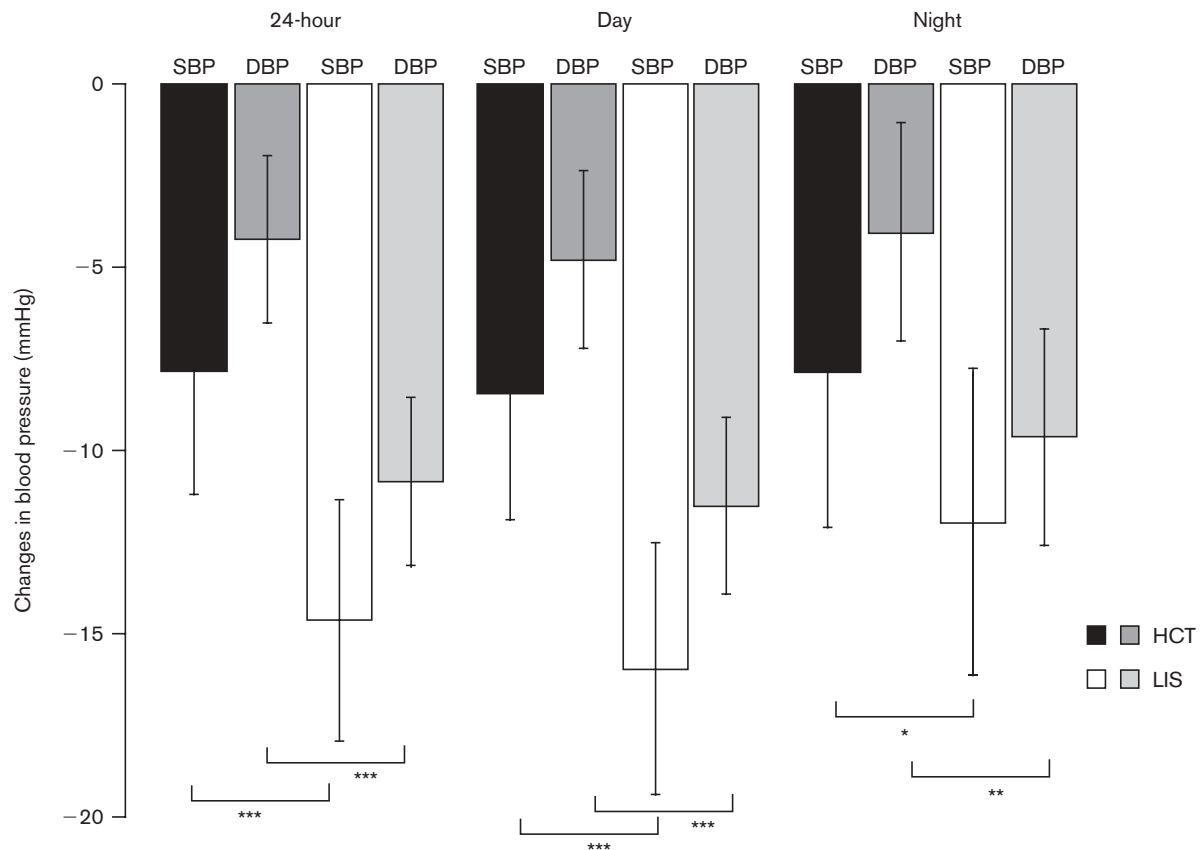
Taken together, the results of the present crossover study show that both the ACE inhibitor and the diuretic significantly reduce daytime and night-time mean ambulatory blood pressure in hypertensive patients of African descent. However, the decrease in ambulatory blood pressure was greater with the ACE inhibitor than with the diuretic. Moreover, differential effects were observed in men and women: men responded better to the ACE inhibitor than to the diuretic, whereas women responded similarly to both classes.

The first original observation of this study is the better blood pressure response to the ACE inhibitor than to the diuretic in a group of African hypertensive patients. Indeed, although our observation is consistent with two crossover studies of the major classes of antihypertensive drugs performed recently in Caucasian populations

[11,19], it is commonly accepted that in black hypertensive patients, diuretics and calcium-channel blockers are more effective antihypertensive agents than blockers of the renin–angiotensin system, owing to the lower-renin and more salt-sensitive hypertension of black hypertensives. In this respect, several studies have reported a poor response to ACE inhibition in Africans [20–25], in African-Americans [3,26–28] and in other black patients with uncomplicated essential hypertension [29]. Yet other investigators have obtained a significant blood pressure reduction with the administration of an ACE inhibitor in African-Americans as well as in black non-Americans [30–37].

Several factors could account for the variability of the blood pressure response to ACE inhibition in black populations. One of them could be the dose of the ACE inhibitor. Indeed, Weir *et al.* [9,38] have suggested that higher doses of ACE inhibitors may actually overcome the racial differences in responsiveness. The second important factor is the sodium intake. A reduction in salt intake has been shown repeatedly to enhance the efficacy of antihypertensive drugs, and particularly that of ACE inhibitors, whatever the race of the patient [9,39,40]. Thus, African-American hypertensive patients do respond to the blockade of the renin–angiotensin system when salt depletion is induced either by the administration of a diuretic [3] or by the administration of a low-salt diet [9]. Unfortunately, most trials investigating the antihypertensive efficacy of ACE inhibitors in individuals of African descent provide no information on sodium intake. It is therefore impossible to distinguish a resistance to the

Fig. 2



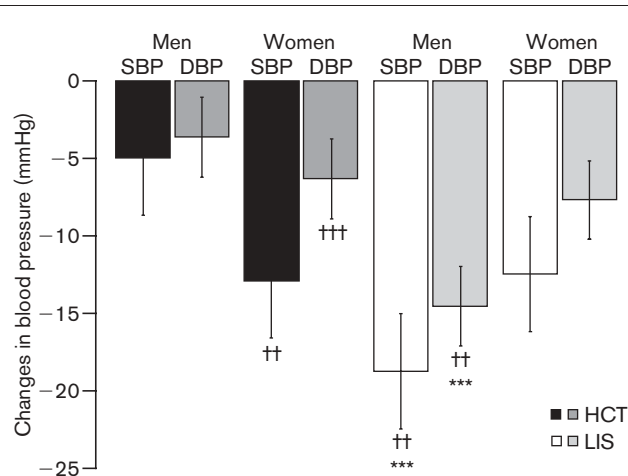
Diurnal changes in ambulatory blood pressure (SBP, systolic blood pressure; DBP, diastolic blood pressure) in response to hydrochlorothiazide (HCT) and to lisinopril (LIS). Both men and women were included in this figure. *P* values compare the response to HCT with the response to LIS during the same time period. \**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001. The error bars represent the 95% confidence intervals adjusted for multiple testing.

ACE inhibitor due to an elevated dietary salt intake, which offsets the effect of ACE inhibition, with a true resistance to ACE inhibition. In the present study, sodium intake was evaluated according to the average 24-h urinary sodium excretion before starting the anti-hypertensive treatment. To our surprise, even in the absence of specific recommendation, it indicated that our patients had a moderate dietary salt intake of approximately 6 g of salt/day, which corresponds to the current guidelines [41]. Hence, the good blood pressure response to ACE inhibition observed in our black patients may be explained by the rather low salt intake.

It is also interesting to note that several crossover studies have actually found ACE inhibitors to provide a greater blood pressure reduction than diuretics in Caucasian hypertensive patients [11,42], whereas large prospective trials generally found either little or no difference between the average blood pressure response to ACE inhibitors and diuretics [43,44]. The ALLHAT trial has even suggested that diuretics can

decrease BP more than ACE inhibitors in a population including a large subgroup of African-Americans [45]. The study design may thus represent another factor leading to discrepant results. Large clinical trials are generally conducted using a parallel design according to which different patient groups received the different drugs under investigation. This study design is certainly convenient for large clinical trials but it may not be the most adequate to investigate the therapeutic efficacy of various antihypertensive strategies. Indeed, the mean decrease in blood pressure obtained in a group of hypertensive patients receiving a given therapy may be less representative, and of little use for the practising physicians. In contrast, studies using a crossover design, in which each patient receives the different drug classes, more closely imitate the strategy used in clinical practice and provide information on the true individual responsiveness. Therefore, studies with a crossover design may produce results that may be more useful than those obtained from parallel-study designs [46].

Fig. 3



Daytime ambulatory blood pressure (SBP, systolic blood pressure; DBP, diastolic blood pressure) response to hydrochlorothiazide (HCT) and lisinopril (LIS) by gender. \*\*\*:  $P < 0.001$  for the difference in response between HCT and LIS. ††:  $P < 0.01$ , †††:  $P < 0.001$  for the difference in response between men and women, respectively. The error bars represent 95% confidence intervals corrected for multiple testing.

The second observation of our study is that gender was the main predictor of the response to treatment, even after controlling for possible confounding factors such as age and drug sequence allocation. To our knowledge, only one study, performed in obese hypertensive patients, has reported similar gender differences in the ambulatory blood pressure response to LIS and HCT [26]. Several previous crossover studies have compared the antihypertensive efficacy of a diuretic with that of an ACE inhibitor, but these studies were either not large enough to stratify their results by gender [10,19,47,48], or did not provide results by gender [11,49]. Similarly, most large trials have not shown significant blood pressure differences between men and women regarding blood pressure response. But again, as discussed previously, these trials were conducted using

a parallel design which considers only the average office blood pressure response to treatment and not the responsiveness by gender.

An additional strength of our study is the electronic monitoring of drug adherence for a subgroup of participants. Drug adherence is an important parameter which is not always taken into account in clinical studies, but which may affect the interpretation of the clinical results. Since a low adherence to drug therapy had been measured previously in another study conducted in the Seychelles [18], we thought that the electronic monitoring of drug adherence would be of importance in the present study. The use of electronic monitors has enabled us to analyse the antihypertensive efficacy of the ACE inhibitor and of the diuretic, as well as the gender effect, according to the percentage of drugs actually taken. Interestingly, the antihypertensive effect of both drugs was of similar magnitude in patients with compliance to drug therapy greater than 90%, and the differences in achieved blood pressure between ACE inhibitors and diuretics could be confirmed. Moreover, because we could observe similar gender differences in blood pressure responses to both drugs among participants with a compliance greater than 90%, we are confident that the differential blood pressure responses to treatment between men and women are not solely due to differences in compliance. However, some slightly lower response of HCT in men due to lower compliance to HCT cannot be excluded as men were, on average, slightly less compliant under the diuretic than under the ACE inhibitor. Whether this is due to the occurrence of diuretic-induced side-effects, such as sexual dysfunction, can not be ascertained from our study.

### Perspective

The results of the present study demonstrate that hypertensive individuals of East African descent with a moderate salt intake have a better ambulatory blood pressure response to 20 mg lisinopril than 25 mg hydro-

**Table 2 Univariate and multivariate relationship between mean daytime ambulatory blood pressure and selected factors in persons under either hydrochlorothiazide or lisinopril**

Selected variables	Hydrochlorothiazide (n = 52)			Lisinopril (n = 52)		
	Coefficient	95%CI	P value	Coefficient	95%CI	P value
<b>Univariate</b>						
Gender (m:0, f:1)	4.44	(0.68–8.20)	0.02	-6.71	[(-10.60)–(-2.82)]	<0.001
Age (by 10 years)	2.11	(0.20–4.01)	0.03	-0.61	[(-2.78)–1.56]	0.58
BMI (kg/m <sup>2</sup> )	0.23	[(-0.29)–0.76]	0.38	-0.28	[(-0.85)–0.29]	0.33
Urinary Na (by 10 mmol/24 h)	0.02	[(-0.32)–0.37]	0.89	0.04	[(-0.34)–0.42]	0.83
<b>Multivariate</b>						
Gender (m:0, f:1)	3.76	[(-0.17)–7.70]	0.06	-6.90	[(-11.17)–(-2.64)]	0.002
Age (by 10 years)	0.16	[(-0.04)–0.35]	0.11	0.04	[(-0.17)–0.25]	0.70
BMI (kg/m <sup>2</sup> )	0.17	[(-0.33)–0.68]	0.49	-0.20	[(-0.74)–0.34]	0.46
Urinary Na (by 10 mmol/24 h)	0.01	[(-0.31)–0.34]	0.94	0.10	[(-0.25)–0.45]	0.57
Intercept	-8.36	[(-24.77)–8.05]		18.25	(0.46–36.03)	

CI, confidence interval; BMI, body mass index.

chlorothiazide. This finding challenges once again the frequent claim that African patients respond poorly to ACE inhibition and emphasizes the importance of a modest salt restriction to improve the efficacy of antihypertensive agents, particularly ACE inhibitors. Moreover, our results show a substantial gender-specific difference in the ambulatory blood pressure response to antihypertensive treatments, which may suggest that black men and women could benefit differentially from antihypertensive medications.

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