Antihypertensive Effect of Low-Dose Hydrochlorothiazide Alone or in Combination with Quinapril in Black Patients with Mild to Moderate Hypertension

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In this study, using 24-hour ambulatory blood pressure (BP) monitoring, the authors assessed the potential for BP control using hydrochlorothiazide (HCTZ, 12.5 mg daily), given as a monotherapy over 12 months to 49 black South African patients with mild to moderate hypertension (mean day diastolic blood pressure [DBP] ≥ 90 and < 115 mmHg). Uncontrolled patients received fixed combination of quinapril/HCTZ 10/12.5, 20/12.5, and 20/25 mg, with dose titration at 3 monthly intervals if BP control was not achieved (day DBP < 90 mmHg). Overall, profound and sustained BP reduction was observed at the end of the study. The 24-hour BP decreased from 151 ± 14/98 ± 7 to 136 ± 15/87 ± 9mmHg (p < 0.0001 at end of study vs. baseline); the mean day BP decreased from 155 ± 14/104 ± 7 to 140 ± 15/91 ± 10 mmHg (p < 0.0001 at end of study vs. baseline). The overall control (mean day DBP < 90 mmHg) and response (decrease in day DBP ≥ 10 mmHg) rates were 49% and 61%, respectively. At the end of the study, only 2 patients (4%) remained on treatment with HCTZ. Out of the initial 12 patients controlled on HCTZ at 3 months (12/49, 24%), 5 patients remained controlled at 6 months and only 1 patient at 12 months. In contrast, quinapril/HCTZ combinations maintained their antihypertensive effect up to 9 months, with a significant number of patients (22/49, 45%) requiring the highest dose of the combination (20/25 mg daily). In conclusion, low-dose HCTZ should not be recommended as monotherapy in black patients with mild to moderate hypertension due to the fact that the BP-lowering effect is attenuated already at 6 months of treatment, with most patients requiring the addition of the ACE inhibitor.

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Low-dose thiazide diuretics are widely recommended as first-line antihypertensive therapy in mild to moderate hypertension.[1,2] It has been shown, using ambulatory blood pressure monitoring, that their short-term (3 months) blood pressure–lowering effect as a monotherapy in black South African hypertensives is modest.[3] However, their long-term efficacy in this population is not well established. Also, while angiotensin-converting enzyme inhibitors were shown to be relatively ineffective in this group of patients as monotherapy, the addition of low-dose thiazide diuretics is associated with more marked BP reduction.[4-7]

In this study, using ambulatory blood pressure monitoring in mild to moderate black South African hypertensives (n = 49), we assessed the potential for blood pressure control using a low-dose hydrochlorothiazide (12.5 mg daily) as a monotherapy over 12 months. Uncontrolled patients received additional doses of an ACE inhibitor administered in fixed combinations once daily (quinapril/HCTZ 10/12.5, 20/12.5, and 20/25 mg; Accuretic®, Warner-Lambert), with dose titration at 3 monthly intervals until BP control was achieved (mean day diastolic blood pressure [DBP] < 90 mmHg).

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METHODS

Patient Population

Included were 60 black patients, who were selected among attendees of the outpatient clinic of the Department of Cardiology, Chris Hani Baragwanath Hospital if they met two entry blood pressure criteria: an average sitting DBP ≥ 95 mmHg, measured as a mean of 10 readings over a 30-minute period using a Dinamap device (Critikon 1846 SX Vital Signs Monitor), and a mean daytime ambulatory DBP ≥ 90 mmHg and < 115 mmHg. The BP measurements were therefore free of observer bias. Eleven patients were lost to follow-up prior to study completion.

Results from 49 patients with complete data at baseline and end of study are analyzed in this report. Eligible patients of either sex with essential mild to moderate hypertension, which was either newly diagnosed or not adequately controlled previously, were entered into the study after a 2-week washout of previous antihypertensive medications (for patients not controlled on their current therapy), followed by a 2-week placebo lead-in phase and 12 months of therapy with active medication. Echocardiography was performed at baseline and end of study to assess the effect of the study medication on left ventricular mass and performance.

Exclusion criteria were as follows: pregnant or lactating females, DBP ≥ 115 mmHg, systolic BP > 200 mmHg, secondary hypertension, myocardial infarction or cerebrovascular accident within the 6 months preceding enrollment, type I and poorly controlled type II diabetes mellitus, acute or chronic heart failure, unstable angina or significant aortic stenosis, clinically significant alteration in renal or liver function, electrolyte abnormalities, history of alcohol or drug abuse, uncooperative or antagonistic personality, and history of hypersensitivity to ACE inhibitors.

All patients gave written informed consent before enrollment. The trial protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand and the Pharmacy and Therapeutics Committee of Chris Hani Baragwanath Hospital.

Study Design

This single-center study comprised three phases: (1) a 2-week drug-free washout period, (2) a 2-week placebo run-in phase to identify placebo responders, and (3) a 12-month prospective open-label titration period. All eligible patients were started on hydrochlorothiazide 12.5 mg daily; 24-hour ABPM was performed every 3 months, and if BP control was not achieved (mean daytime ambulatory DBP < 90 mmHg), treatment was adjusted as follows: quinapril/HCTZ 10/12.5 mg, quinapril/HCTZ 20/12.5 mg, and quinapril/HCTZ 20/25 mg (two tablets of 10/12.5 mg) once daily.

Compliance assessment by tablet count was performed at each visit. All patients fell within the 80% to 120% range throughout the study.

Blood Pressure Measurement

Office BP was measured following the recommendations of the American Heart Association.[8]

By using the Dinamap Critikon 1846 SX vital signs monitor, BP was measured every 3 minutes for up to 30 minutes. The monitors were calibrated against mercury sphygmomanometers, with a maximum acceptable difference of ± 5 mmHg at 200 mmHg.[9] The reason for using the Dinamap as a screening device was to eliminate as much as possible observer bias and white-coat hypertension.

Then, 24-hour ABPM was measured using SpaceLabs 90207 oscillometric BP monitors calibrated against a mercury sphygmomanometer before use in each patient with monitor readings being within 3 mmHg or 2% of the manometer readings, whichever was greater.[10] Monitors were programmed to read blood pressure and heart rate every 15 minutes from 0600 h to 1800 h and every 20 minutes from 1800 h to 0600 h. Mean daytime (0600 h to 1800 h) and nighttime (1800 h to 0600 h) BP and HR were calculated.

Trough-to-Peak Ratio Measurement Using ABPM

The average of 2 consecutive hours of maximum BP lowering during the day was defined as peak effect. The average of the last 2 hours of the 24-hour period was defined as the trough effect. Trough-to-peak ratios were calculated for systolic and diastolic BP. This analysis included only responding patients as the calculation of trough-to-peak ratios in nonresponding patients is of no clinical value and is misleading in many instances (response—decrease in mean day DBP ≥ 10 mmHg).

Echocardiography and Doppler Analysis

M-mode and two-dimensional echocardiograms were obtained with the Hewlett Packard Sonos 2500 system

Table I Demographic Data (n = 49)

Age (years)	54 ± 10
Sex (female/male)	37/12 (75.5% female)
Body mass index (kg/m^2)	31 ± 6
Diabetes mellitus (type 2)	8/49
Microalbuminuria (> 30 mg/24 h)	15/46
Total cholesterol (> 5.5 mmol/l)	9/44
Glomerular filtration rate (ml/min/1.73 m^2)	87 ± 22
Dinamap blood pressure (SBP/DBP, mmHg)	167 ± 18/102 ± 8
24-hour blood pressure (SBP/DBP, mmHg)	151 ± 14/98 ± 7
Daytime blood pressure (SBP/DBP, mmHg)	155 ± 14/104 ± 7
Nighttime blood pressure (SBP/DBP, mmHg)	146 ± 15/92 ± 9

SBP, systolic blood pressure; DBP, diastolic blood pressure.

using a 2.5 MHz transducer. Each patient was examined in the left lateral position. M-mode echocardiography of the left ventricle was performed in the short axis view.[11] M-mode variables were analyzed according to the American Society of Echocardiography convention[12] and included LV end-diastolic (LVEDD) and end-systolic diameters (LVESD) and septal and posterior wall thickness. All measurements were recorded on videotape and analyzed by the same experienced echocardiographer who was blinded to the BP and clinical data of the patient. The LV mass was derived according to an anatomically validated regression method that corrects LV mass estimates obtained from the American Society of Echocardiography measurements.[13]

Glomerular Filtration Rate and Microalbuminuria Excretion Rate

Glomerular filtration rate (GFR) using 51Cr-EDTA was measured in all patients at baseline and end of study. Microalbumin excretion rate and creatinine clearance were measured on 24-hour urine sample at baseline and end of study.

Statistical Analysis

Results are presented as mean ± standard deviation. Continuous data were analyzed using Student's t-test for paired observations. When no proof of normality was available, nonparametric tests (i.e., Wilcoxon's matched-pairs signed-rank test and the Mann-Whitney U test) were used for between- and within-group comparisons. A p-value of < 0.05 was considered significant for all statistical tests.

RESULTS

Antihypertensive Effects

Table I summarizes the baseline demographic characteristics and blood pressure profile for the study population. The patients were mostly females (54 ± 10 years) of high body mass index. Thirteen patients had BMI greater than 35 kg/m^2 with marked obesity. Both Dinamap and 24-hour ambulatory measurements confirmed mild to moderate hypertension in these patients (in a matched group of 40 normotensive subjects, the mean 24-hour ambulatory BP was 120 ± 8/75 ± 6 mmHg, with daytime BP 124 ± 8/81 ± 6 mmHg and nighttime BP 115 ± 9/70 ± 7 mmHg).

Table IIa describes the change in BP from baseline and at each 3-month titration point with the corresponding control (daytime mean DBP < 90 mmHg) and response (decrease in mean day DBP ≥ 10 mmHg) rates. The 24-hour BP profiles for responding patients are shown in Figure 1. The overall BP-lowering effect was significant and marked. The 24-hour systolic BP decreased by 15 mmHg and the diastolic BP by 11 mmHg. This resulted in an overall control rate of 49% and response rate of 61%; 24-hour heart rate did not change significantly (74 ± 9 bpm at baseline vs. 75 ± 9 bpm at end of study). These findings are consistent with the office BP measurements performed with the Dinamap (Table IIb). The BP decreased from 167 ± 18/102 ± 8 mmHg to 142 ± 19/88 ± 10 mmHg. The response rate (diastolic BP reduction ≥ 10 mmHg) was 55%, with the control rate for DBP ≤90 mmHg of 55% and for DBP ≤85 mmHg of 41%.

Table III shows that at the end of the study, only 2 patients (4%) remained on treatment with HCTZ (only

Table IIa Change in Blood Pressure with Hydrochlorothiazide or Quinapril/HCTZ Combinations with Control (day mean DBP < 90 mmHg) and Response (decrease in day mean DBP ≥ 10 mmHg) Rates (n = 49)

Period	24-Hour BP (mmHg)	Day BP (mmHg)	Night BP (mmHg)	Control Rate	Response Rate	Control and Response
Baseline	151 ± 14/98 ± 7	155 ± 14/104 ± 7	146 ± 15/92 ± 9			
3 months	140 ± 12/91 ± 9	144 ± 12/97 ± 9	136 ± 14/85 ± 9	12/49 (24%)	20/49 (41%)	8/49 (16%)
6 months	137 ± 12/88 ± 8*	140 ± 13/94 ± 9*	133 ± 14/83 ± 8*	16/49 (33%)	22/49 (45%)	14/49 (29%)
9 months	137 ± 14/89 ± 9*	140 ± 14/93 ± 9*	134 ± 17/84 ± 10*	17/49 (35%)	24/49 (49%)	11/49 (22%)
12 months	136 ± 15/87 ± 9*	140 ± 15/91 ± 10*	132 ± 16/82 ± 9*	24/49 (49%)	30/49 (61%)	21/49 (43%)

*p < 0.0001 at 6, 9, and 12 months versus baseline.

Table IIb Change in Dinamap Blood Pressure at 3 Months of Therapy with Hydrochlorothiazide 12.5 mg Daily and at 12 Months of Therapy with Quinapril/HCTZ Combination and Corresponding Control (mean DBP ≤90 mmHg and ≤85 mmHg) and Response (mean DBP reduction ≥ 10 mmHg) Rates after 12 Months of Treatment (n = 49)

Period	Dinamap BP (mmHg)	Control (DBP ≤90 mmHg)	Control (DBP ≤85 mmHg)	Response
Baseline	167 ± 18/102 ± 8			
3 months	151 ± 17/94 ± 9	15/49 (31%)	8/49 (16%)	21/49 (43%)
6 months	147 ± 21/91 ± 10	19/49 (39%)	12/49 (24%)	24/49 (49%)
9 months	144 ± 19/90 ± 10	21/49 (43%)	14/49 (29%)	24/49 (49%)
12 months	142 ± 19/88 ± 10	27/49 (55%)	20/49 (41%)	27/49 (55%)

DBP, diastolic blood pressure.

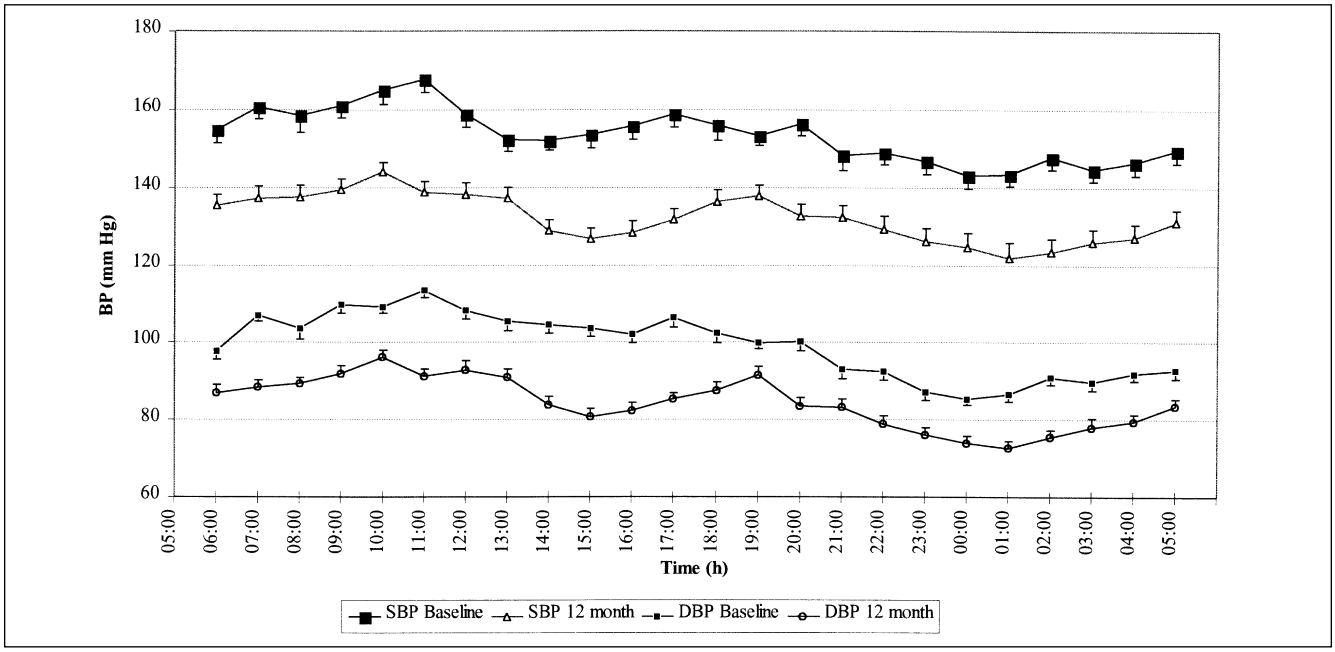

Figure 1. Blood pressure profiles at baseline and end of study for responding (daytime DBP decrease of > 10 mmHg) patients (n = *29) on quinapril/HCTZ combination. DBP, diastolic blood pressure; SBP, systolic blood pressure.*

Table III Patient Control (mean daytime DBP < 90 mmHg) and Response (reduction in mean day DBP ≥ 10 mmHg) Rates after 12 Months of Treatment with Hydrochlorothiazide or Quinapril/HCTZ Combination

Patient Group (n = 49)	HCTZ 12.5 mg (n = 2)	Accuretic 10/12.5 mg (n = 15)	Accuretic 20/12.5 mg (n = 10)	Accuretic 20/25 mg (n = 22)	Total
Response	1 (2%)	10 (20%)	8 (16%)	11 (22%)	30 (61%)
Controlled	1 (2%)	12 (24%)	6 (12%)	5 (10%)	24 (49%)
Not controlled	1 (2%)	3 (6%)	4 (8%)	17 (35%)	12 (51%)

DBP, diastolic blood pressure.

1 controlled), 15 patients (31%) were on Accuretic 10/12.5 mg (12 controlled), 10 patients (20%) were on Accuretic 20/12.5 mg (6 controlled), and the remaining 22 patients (45%) required Accuretic 20/25 mg (5 controlled).

Table IV documents for the first time using ABPM methodology that the initial modest BP-lowering effect of low-dose thiazide diuretic noted at 3 months (12/49 patients, 24% controlled) was not sustained. Out of the initial 12 patients controlled on HCTZ at 3 months, 5 patients (5/12, 42%) remained controlled at 6 months and only 1 patient (1/12, 8%) at 12 months. In other words, only 2% (1/49) of patients treated with low-dose thiazide diuretic may be expected to be controlled after 1 year of therapy. In contrast, the quinapril/HCTZ combinations maintained their antihypertensive effect up to 9 months, with a significant number of patients (22/49 patients, 45%) requiring quinapril/HCTZ 20/25 mg. Out of the 15 patients treated with quinapril/HCTZ 10/12.5 mg for up to 9 months, 12 remained controlled at the end of the treatment period.

The calculations of systolic and diastolic through-to-peak ratios are shown in Figure 2. Combination therapy achieved adequate trough-to-peak ratios for both systolic and diastolic BP in responding patients (0.56 and 0.58, respectively).

Echocardiographic Data

Patients were divided into two groups according to the presence of left ventricular hypertrophy (LVH, LVMI > 110 g/m^2, n = 13) or absence of LVH (n = 11) at baseline.

Table IV Blood Pressure Profiles and Patient Control (mean daytime DBP < 90 mmHg) and Response (reduction in mean day DBP ≥ 10 mmHg) Rates after 12 Months of Treatment with Hydrochlorothiazide (12.5 mg)

Patient Group (n = 49)	Baseline	3 Months	6 Months	9 Months	12 Months
Response		20/49 (41%)	5/49 (10%)	2/49 (4%)	1/49 (2%)
Control		12/49 (24%)	5/49 (10%)	2/49 (4%)	1/49 (2%)
Control and response		8/49 (16%)	4/49 (8%)	1/49 (2%)	1/49 (2%)
Response					
24-hour SBP/DBP	151 ± 17/98 ± 7	137 ± 10/86 ± 6			
Day SBP/DBP	155 ± 14/104 ± 7	139 ± 11/91 ± 6			
Night SBP/DBP	146 ± 15/92 ± 9	133 ± 11/80 ± 7			
Controlled					
24-hour SBP/DBP		133 ± 9/81 ± 5			
Day SBP/DBP		136 ± 10/85 ± 14			
Night SBP/DBP		131 ± 11/76 ± 6			
Control and response					
24-hour SBP/DBP		132 ± 9/80 ± 4			
Day SBP/DBP		135 ± 12/85 ± 5			
Night SBP/DBP		129 ± 10/75 ± 7			

SBP, systolic blood pressure; DBP, diastolic blood pressure.

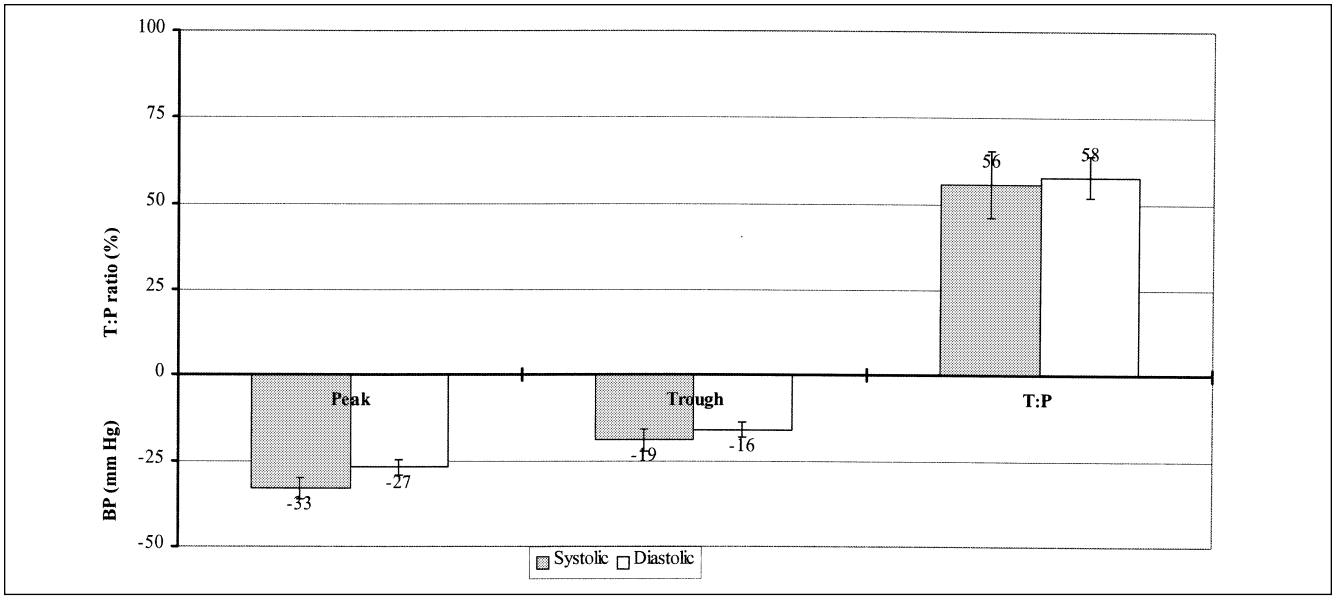

Figure 2. Trough and peak effect and T:P ratios in responding (daytime DBP decrease > 10 mmHg) patient (n = *29) after 12 months of treatment with quinapril/HCTZ combination. DBP, diastolic blood pressure.*

At 12 months, there was a 13% decrease in LV mass index in the group of patients with LV hypertrophy (from 146 ± 27 to 125 ± 30 g/m^2) versus a 5% increase in LVMI in the group of patients without LV hypertrophy at baseline (from 89 ± 12 to 93 ± 20 g/m^2) ($p = 0.05$ at 12 months for the group with LV hypertrophy vs. the group without LV hypertrophy). Furthermore, a decrease in LVMI of greater than 10% was achieved in 7/13 patients (54%) in the group with LVH versus 4/11 patients (36%) in the group without LVH at baseline.

Safety and Tolerability

Table V shows the effect of therapy on the biochemical parameters. It is important to note that the potassium level remained unchanged. Plasma glucose concentration and lipids did not change significantly. The observed 11% decrease in glomerular filtration rate was expected with ACE inhibitor therapy and is of no clinical significance. There was a decrease in the number of patients with microalbuminuria at the end of the study compared to baseline. However, the results do not differ from random observations by Fisher's exact test ($p = 0.0349$).

Both hydrochlorothiazide and quinapril/HCTZ were well tolerated. Most adverse events were mild and transient, the most common being cough, upper respiratory infection, and general body aches and fatigue. There were no serious adverse events or deaths observed.

DISCUSSION

The major findings of the study are the following:

1. In black South African patients with mild to moderate hypertension, low-dose thiazide diuretics should not be recommended as monotherapy due to the fact that the BP-lowering effect is markedly attenuated already at 6 months of treatment, with most patients requiring the addition of the ACE inhibitor.
2. Therapy with quinapril/HCTZ combinations lowers blood pressure significantly, with control achieved in 49% of patients and a response rate of 61%. This effect was adequately maintained over 24 hours with systolic and diastolic T:P ratios in responding patients of 0.56 and 0.58, respectively. The antihypertensive efficacy of the combination was maintained for up to 9 months of treatment, unlike that of low-dose thiazide diuretics.
3. All three HCTZ/quinapril combinations used were of clinical value. The starting low-dose combination (10/12.5 mg) achieved BP control in half of the 24 controlled patients at the end of the study, while the combination 20/12.5 mg achieved control in further 25% of this group of patients.
4. The effect of therapy on left ventricular mass index was noticeable among the patients with left ventricular hypertrophy at baseline. In this group, a 13% reduction in LVMI at 12 months was observed versus a 5% increase in LVMI in patients without LV hypertrophy at baseline ($p = 0.05$).

Table V Changes in Laboratory Parameters after 12 Months of Treatment with Hydrochlorothiazide or Quinapril/HCTZ Combination

Parameter	Baseline	12 Months
Biochemistry		
Sodium (mmol/l)	140 ± 3	139 ± 4
Potassium (mmol/l)	4.0 ± 0.6	3.9 ± 0.6
Urea (mmol/l)	4.1 ± 0.4	4.2 ± 1.5
Creatinine (μmol/l)	79 ± 17	80 ± 16
Glucose (mmol/l)	4.5 ± 0.8	4.8 ± 1.0
Lipid profile		
Total cholesterol (mmol/l)	4.7 ± 1.2	5.0 ± 1.4
Triglycerides (mmol/l)	1.6 ± 0.9	1.7 ± 1.0
HDL (mmol/l)	1.3 ± 0.4	1.4 ± 0.6
LDL (mmol/l)	2.7 ± 1.2	2.7 ± 1.2
Renal function tests		
GFR (ml/min/1.73 m^2)	87.0 ± 23.5	76.6 ± 18.3*
Creatinine clearance (ml/min)	87.0 ± 32.9	83.1 ± 42.3
Microalbuminuria (mg/24 h)	27.4 ± 49.7	14.6 ± 13.2
Microalbuminuria (*n*, > 30 mg/24 h)	15	10

*$p < 0.05$ at end of study versus baseline.

5. The biochemical parameters did not change significantly, except for a slight expected decrease in GFR and a reduction in 24-hour albumin excretion rate.
6. The study drugs were well tolerated, with no serious adverse events or deaths.

Thiazide diuretics have long been recommended and used as a first-line therapy in the management of mild to moderate hypertension. However, their efficacy as a monotherapy is, at best, modest. Materson et al[14,15] showed that in young African American patients with mild to moderate hypertension, office DBP of less than 90 mmHg at 1 year was achieved only in 42% of patients, using 12.5 to 50 mg of HCTZ. Furthermore, using the low-dose HCTZ (12.5 mg), the above goal was reached in only 35% of patients. The present study should be viewed bearing in mind its limitations: the dose of HCTZ was not increased to 25 mg, and predominantly obese hypertensive women were enrolled. Using 24-hour ambulatory blood pressure monitoring, we found that a low-dose thiazide diuretic achieved BP control in only 24% of the patients at 3 months, with a response rate of 41%, but most of these patients required addition of the ACE inhibitor to achieve BP control. This discrepancy may be partly explained by the fact that in our study, the baseline office BP, measured by Dinamap, was higher, measuring 167 ± 18/101 ± 8 mmHg, and also by the fact that we did not increase the dose of the thiazide diuretic above 12.5 mg daily. Therefore, it is advisable to repeat BP measurements in patients controlled on monotherapy with low-dose thiazide diuretics at less than 3-month intervals to identify patients requiring additional antihypertensive medications.

Previous studies have shown that black hypertensive patients respond less well to angiotensin-converting enzyme inhibitors than whites,[16] perhaps because of different pathophysiological factors that characterize their hypertensive disease.[17,18] However, the addition of hydrochlorothiazide significantly enhances their antihypertensive efficacy.[7,19] In this study, the combination ACE inhibitor/thiazide diuretic reduced blood pressure significantly and achieved BP control in 49% of patients. This effect was maintained throughout the 24-hour period, with systolic and diastolic trough-to-peak effect of 56% and 58%, respectively. These data support the recommendation to start treatment with a combination of an ACE inhibitor and low-dose thiazide diuretic. This is consistent with the latest JNC VI recommendation that it is appropriate to use such a low-dose combination therapy as an initial step. The rationale behind such an approach is not only to achieve better BP control but also to achieve better end-organ protection, conferred mainly by the ACE inhibitor.

The importance of BP control was highlighted by the recent report of the Hypertension Optimal Treatment Trial.[20] The results of this trial suggest that the optimal

target DBP for antihypertensive therapy should be 83 mmHg. In our trial, 41% of patients had DBP ≤ 85 mmHg at 1 year, measured in the office by Dinamap oscillometric devices.

Left ventricular hypertrophy is the strongest predictor of cardiovascular morbidity and mortality other than age.[21] Black hypertensive patients are a high-risk group of patients with regard to development of target organ damage, especially LV hypertrophy.[22] It has been shown recently that regression of LV hypertrophy by antihypertensive therapy is associated with better long-term cardiovascular outcome.[23,24] In the present study, we observed differences in the response of the LV mass index to therapy according to the presence or absence of LV hypertrophy at baseline.

The combination therapy used in our study was shown to affect favorably microalbuminuria, with no adverse metabolic side effects. The treatment was well tolerated, with most adverse events being mild and transient. Chronic cough was observed throughout the study but was tolerated by the patients and did not require cessation of medication. The higher incidence of upper respiratory tract infections may be explained by the poor socioeconomic and living conditions of these patients (poverty, undernutrition, overcrowding, etc.).

In conclusion, our findings suggest that low-dose thiazide diuretics should not be recommended as monotherapy in black patients with mild to moderate hypertension due to the fact that their long-term BP-lowering effect is markedly attenuated, with most patients requiring the addition of the ACE inhibitor.

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