Original Article

Effectiveness of chlorthalidone/amiloride versus losartan in patients with stage I hypertension: results from the PREVER-treatment randomized trial

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Objectives: To compare the blood pressure (BP)-lowering efficacy of a chlorthalidone/amiloride combination pill with losartan, during initial management of stage I hypertension.

Methods: In a randomized, double-blind, controlled trial, 655 participants were followed for 18 months in 21 Brazilian academic centers. Trial participants were adult volunteers aged 30–70 years with stage I hypertension (BP 140–159 or 90–99 mmHg) following 3 months of a lifestyle intervention. Participants were randomized to 12.5/2.5 mg of chlorthalidone/amiloride ($N = 333$) or 50 mg of losartan ($N = 322$). If BP remained uncontrolled after 3 months, study medication dose was doubled, and if uncontrolled after 6 months, amlodipine (5 and 10 mg) and propranolol (40 and 80 mg twice daily) were added as open-label drugs in a progressive fashion. At the end of follow-up, 609 (93%) participants were evaluated.

Results: The difference in SBP during 18 months of follow-up was 2.3 (95% confidence interval: 1.2 to 3.3) mmHg favoring chlorthalidone/amiloride. Compared with those randomized to diuretic, more participants allocated to losartan had their initial dose doubled and more of them used add-on antihypertensive medication. Levels of blood glucose, glycosilated hemoglobin, and incidence of diabetes were no different between the two treatment groups. Serum potassium was lower and serum cholesterol was higher in the diuretic arm. Microalbuminuria tended to be higher in patients with diabetes allocated to losartan (28.5 ± 40.4 versus 16.2 ± 26.7 mg, $P = 0.09$).

Conclusion: Treatment with a combination of chlorthalidone and amiloride compared with losartan yielded a greater reduction in BP.

Clinical trials registration number: NCT00971165.

Keywords: amiloride, chlorthalidone, drug treatment, hypertension, losartan

Abbreviations: ACEi, angiotension-converting enzyme inhibitor; ARB, angiotensin receptor blocking; BP, blood pressure; CVD, cardiovascular disease; LDL, low-density lipoprotein; RCT, randomized controlled clinical trial

INTRODUCTION

Cardiovascular disease (CVD) represents the most common cause of death worldwide [1]. High blood pressure (BP) is the most important risk factor for CVD [2] because of its risk profile [3] and high prevalence [4]. Hypertension is highly prevalent in Brazil [5,6]. The efficacy of drug treatment to prevent major CVD events in

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patients with hypertension has been repeatedly demonstrated in double-blind randomized controlled clinical trials (RCTs). The comparative effectiveness of BP-lowering drugs has also been investigated in RCTs, which have demonstrated no definitive superiority for agents from any drug class [7,8]. With the exception of ALLHAT [9] and the INSIGHT trial [10]; however, few RCT have compared the efficacy of agents from other BP-lowering classes with diuretics. In the ALLHAT trial, lisinopril and amlodipine were not superior to chlorthalidone in the prevention of combined fatal coronary heart disease (CHD) or nonfatal myocardial infarction (primary outcome), or all-cause mortality, and chlorthalidone was superior to lisinopril and amlodipine in the prevention of other major cardiovascular events, especially heart failure.

Angiotensin receptor blocking (ARB) agents are reputed to provide additional non-BP-related benefits that may be especially valuable in patients with renal disease and diabetes. They have been preferentially recommended for treatment of patients with these conditions in several BP management guidelines [11–13]. Recent reviews and RCT meta-analyses, however, have raised concerns regarding the efficacy and safety of ARB agents [14–18]. Large RCTs designed to compare ARB agents with placebo, in addition to usual treatment, have failed to demonstrate that ARB agents provide additional CVD protection and some have even suggested worse renal outcomes with these agents [14]. In addition, four RCT meta-analyses that compared ARB with other antihypertensive drug classes or placebo have raised the possibility that ARB agents might be ineffective in the prevention of all-cause mortality and other major CVD outcomes in older persons and in patients with diabetes or hypertension [15–18].

There has been no head-to-head comparison between diuretics and ARB agents in the prevention of clinical cardiovascular events and BP-lowering effects, and, as far as we know, effects on surrogate endpoints [19]. Based on this important shortfall in knowledge, we conducted a randomized, double-blind, multicenter clinical trial, designed to compare the BP-lowering efficacy of chlorthalidone in combination with amiloride with losartan, for the initial management of hypertension in patients with stage I hypertension.

METHODS

Study design

This study was registered at clinicaltrials.gov (NCT00971165) and its rationale and methods have been published elsewhere [20]. Briefly, the PREVER-treatment study was a randomized double-blind controlled trial of chlorthalidone along with amiloride versus losartan for the management of stage I hypertension. The study was conducted in 21 academic medical centers in Brazil. Participants, members of the steering committee, healthcare staff, data collectors, and outcome assessors but not members from the data safety monitoring committee were blinded as to whether patients received chlorthalidone/amiloride or losartan. The trial was designed by the Steering Committee. The study was approved by the Research Ethics Board of the institution each participant belonged to.

Participants

To be eligible, volunteers had to be between 30 and 70 years of age, with stage I hypertension (average SBP 140–159 mmHg or DBP 90–99 mmHg) and no current use of BP-lowering medication. Exclusion criteria included a history of intolerance to any of the study medications, a compelling indication for diuretic or ARB therapy, and pregnancy.

Procedures

During an initial lifestyle intervention phase, all potentially eligible participants were counseled in weight loss, dietary sodium reduction, adoption of a DASH-type diet, physical activity, and smoking cessation. Those whose BP remained inadequately controlled (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg) after 3 months of lifestyle intervention were enrolled in the RCT.

After written informed consent had been obtained, participants were randomly assigned in a 1 : 1 ratio to a chlorthalidone along with amiloride combination pill or to losartan. Randomization was based on a computer-generated list, using validated software, with variable block sizes of 4, 6, 8, or 10 and was stratified by center. To guarantee concealment of the allocation list, randomization was implemented through a 24-h web-based automated system.

Interventions

The two study drugs were identical in size, shape, color, taste, and texture. Chlorthalidone was chosen as the study diuretic because it had been widely tested in previous RCT and has a longer half-life and greater capacity to lower BP compared with thiazide diuretics such as hydrochlorothiazide [21]. Hypokalemia, which is a recognized side-effect of chlorthalidone, can be avoided by concurrent use of a potassium-sparing agent, such as amiloride [22]. We chose to combine chlorthalidone and amiloride in the same pill. The initial doses of the two study drugs were 12.5/2.5 mg for the chlorthalidone/amiloride combination pill and 50 mg for losartan. At the third month study visit, the dose was doubled if BP remained uncontrolled. If BP was uncontrolled at the 6-month visit, amlodipine 5 mg once a day was added, in an open fashion, and increased to 10 mg if necessary at the 9-month visit. At the 12-month visit, propranolol 40 twice a day was prescribed for patients with uncontrolled BP, and doubled at the fifteenth month visit if necessary.

Outcomes

The primary outcome was difference in mean BP between the two treatment groups during follow-up. The proportion of patients with controlled hypertension, use of nonstudy BP-lowering medications, incidence of adverse events, and development or worsening of microalbuminuria and left ventricular mass estimated by ECG criteria were additional outcomes. Fatal and nonfatal major cardiovascular events were secondary outcomes.

An automatic electronic device Microlife BP 3BTO-A, licensed for fabrication by Micromed Biotecnologia Ltda (Brasília, Brazil), was used to measure BP and an average of two readings at each study visit was used to estimate level of BP. Left ventricular mass was estimated by

electrocardiographic measurements, using the Sokolow–Lyon voltage, voltage-duration product criteria, and the Cornell voltage and voltage-duration product criteria [23,24]. A semiautomated method was developed to measure these indexes.

CVD outcomes were adjudicated using standardized definitions on the basis of participant interviews and hospital charts, death certificates, and verbal autopsy with next of kin, by members of the outcome committee, who were blinded to treatment assignment.

Adverse events were investigated by use of elicited open questions and a semistructured self-reported questionnaire that probed for general symptoms and presumed adverse effects of the study drugs. Laboratory measurements, including serum potassium, uric acid, glycosylated hemoglobin, fasting serum glucose, and serum cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglyceride levels were obtained at the final follow-up visit.

Study oversight

All centers were trained in the implementation of protocol requirements during regional meetings and during an on-site study initiation visit. Study monitoring was accomplished through daily data review of the electronic forms and by periodic on-site monitoring, which was performed at least three times in each center by monitors and twice by the coprincipal investigators. Laboratory quality control was performed by a central laboratory using standard procedures. Inconsistencies in the database were reviewed and resolved in a prompt fashion.

Sample size

The study was originally planned as a test for noninferiority in the BP-lowering effect of the two study treatments, with a *P* alpha of 0.01 and power of 99%, a SBP standard deviation of 12 mmHg, and a maximum acceptable absolute difference of 4 mmHg (systolic). The estimated sample size to meet these requirements was 433 patients per group. We did not meet this sample size goal but were still able to identify a significant difference in BP between the two treatment arms.

Statistical analysis

Trial results were analyzed using the intention-to-treat approach. The comparison of levels of BP between the two treatment groups at each visit was done using *t* test for independent samples and a random-effects linear model, fitted to SBP and DBP, was used to compare BP by treatment group during follow-up. The random-effects model included an intercept and a slope to adjust for the within-participant correlation among the longitudinal data. To examine the change in SBP and DBP, we included in the model an indicator variable for time (baseline, 3, 6, 9, 12, 15, and 18 months), an interaction term for treatment by time, and the variable treatment. A vigorous attempt was made to measure BP in those lost to follow-up at the end of the trial. Results or imputed estimates were included from participants who were lost to follow-up, who had minor protocol deviations, such as missing one or more visits or measurement of only one BP value at a study visit, and whose study visits occurred on days other than scheduled. The rate of BP control by treatment assignment was compared by means of χ^2 testing at the end of trial. The incidence of adverse events in the two treatment groups was also compared by χ^2 testing. Electrocardiographic estimates of left ventricular mass were compared by using analysis of variance for repeated measurements and biochemical parameters were compared by means of Student's *t* test for independent samples. Analyses were repeated with stratification by sex, skin color (whites versus nonwhites), and age (less than and over 55 years). All analyses were also conducted in the prespecified subgroup of patients with diabetes at baseline. All analyses were performed with SPSS, version 21.0 (IBM, Armonk, New York, USA).

RESULTS

Between February 2011 and September 2014, a total of 18 080 individuals were screened at 21 clinical centers for possible participation in the current study and a related PREVER hypertension prevention trial (Fig. 1). Following initial screening, 1772 volunteers were further evaluated for possible participation in the PREVER-treatment trial and 1457 (82%) were entered into a 3-month lifestyle intervention phase. At the end of this phase, 655 volunteers who still met the study inclusion criteria were entered into the trial and randomly assigned to double-blind antihypertensive therapy with chlorthalidone/amiloride ($n = 333$) or losartan ($n = 322$). Overall, 609 (93%) of the 655 trial participants were evaluated at the end of follow-up (18 months). Thirteen (3.9%) patients in the diuretic arm stopped taking the study drug because of an adverse event but eight of them were evaluated at the final visit. In the losartan arm, 15 (4.7%) patients stopped the trial drug, but all were evaluated at the final visit. Four patients in the diuretic arm who had an adverse event and did not return for the final visit reported nonspecific symptoms (malaise, fatigue) and one reported ascites. In total, 27 patients in the diuretic arm and 33 in the losartan arm were not taking their assigned study drug at the month 18 visit, and none crossed over to use the other study drug.

Baseline characteristics of the participants are identified in Table 1. In general, there was a similar distribution of characteristics in both the treatment arms. Mean age of the study sample was 54 years, with an almost equal number of men and women participants. Approximately two-thirds were white and one-third were nonwhite. Both treatment groups had an average of more than 10 years of education. Their mean SBP and DBP were approximately 142 and 90 mmHg, respectively. Their BMI was approximately 29 kg/m^2, with about one-third being obese. Few study participants were current smokers but about two-thirds reported current consumption of alcoholic beverages. There were no patients with previous CVD because this was an exclusion criterion. About one-third of the participants had previously been treated with an angiotensin-converting enzyme inhibitor (ACEi) and one-third with an ARB.

There was a significantly greater reduction in SBP during follow-up in those allocated to the diuretic arm: 2.3 (95% confidence interval: 1.2 to 3.3, $P < 0.001$) mmHg (Fig. 2).

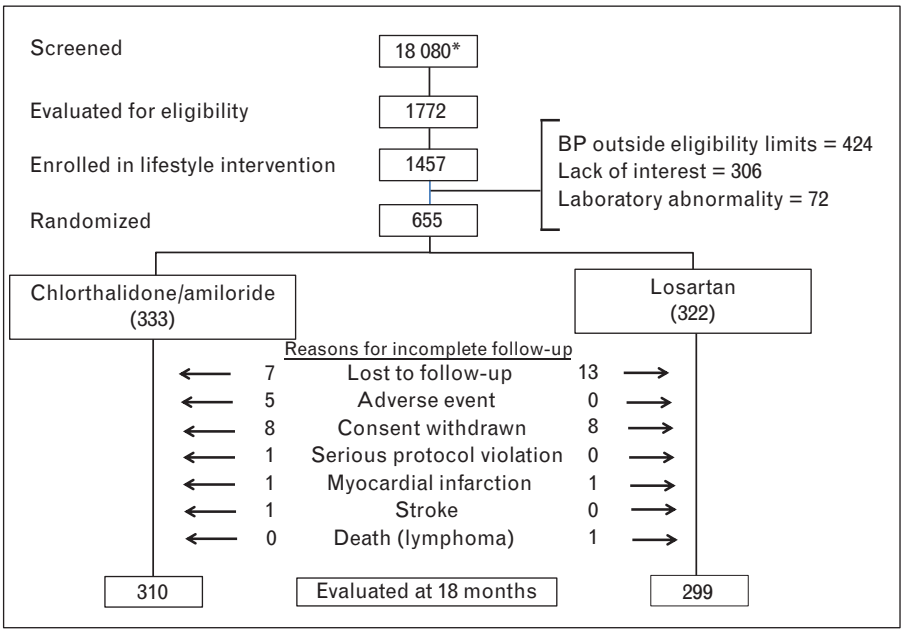

FIGURE 1 Study flow diagram. *Patients were concurrently screened to participate in either the PREVER-treatment or PREVER-prevention trial.

The curves started to diverge by the 6-month visit, at a time when most patients were being treated with the full dose of their study drug. During follow-up, a higher percentage of those allocated to chlorthalidone/amiloride (48%) were maintained on the initial dose of their study drug compared with the losartan group (39.7%). In addition, more patients in the losartan arm were treated with open-label amlodipine and propranolol. At the end of the trial, the average daily dose of amlodipine was 1.2 mg/day in the diuretic arm compared with 1.6 mg/day in the ARB arm. Similarly, the final average dose of propranolol was 0.9 mg/day in the diuretic arm compared with 1.7 mg/day in the ARB arm. In the visit-to-visit between-group comparison, SBP was significantly lower in the diuretic group compared with the ARB group at the 6-month and every subsequent visit, with the difference being greatest at 9 months (3.9 mmHg) and

TABLE 1. Baseline characteristics of the PREVER-treatment trial participants [*N* (%) or mean ± standard deviation]

Characteristics		Chlorthalidone/amiloride (333)	Losartan (322)
Sex	Male	167 (50.2)	167 (51.9)
Age (years)		53.9 ± 8.4	54.7 ± 7.9
Skin color	White	205 (61.6)	198 (61.5)
	Nonwhite	128 (38.4)	124 (38.5)
Education (years)		10.7 ± 4.6	10.5 ± 4.2
SBP (mm Hg)		142.6 ± 7.1	142.1 ± 6.5
DBP (mm Hg)		89.7 ± 6.3	89.4 ± 6.1
BMI (kg/m^2)		29.1 ± 5.0	28.8 (4.7)
Obese (BMI ≥ 30)		121 (36.3)	111 (34.5)
Cholesterol (mg/dl)		196.8 ± 40.5	193. 2 ± 39.1
LDL-cholesterol (mg/dl)		119.1 ± 36.9	114.7 ± 33.7
HDL-cholesterol (mg/dl)		47.1 ± 11.8	47.9 ± 12.4
Triglycerides (mg/dl)		156.4 ± 96.8	154.0 ± 125.1
Creatinine (mg/dl)		0.80 ± 0.18	0.80 ± 0.19
Diabetes mellitus		47 (14.2)	50 (15.6)
Statin use		92 (27.6)	101 (31.5)
Previous use of ACEi		111 (33.5)	107 (32.5)
Previous use of ARB		122 (36.6)	128 (39.8)
Previous use of diuretic		41 (12.4)	31 (9.6)
Previous use of β-blocker		41 (12.4)	31 (9.6)
Smoking	Current	27 (8.1)	21 (6.5)
	Never	177 (53.2)	181 (56.4)
	Past	129 (38.7)	119 (37.1)
Alcoholic beverage consumption	Current	223 (67.0)	197 (61.2)
	Never	55 (16.5)	63 (19.6)
	Past	55 (16.5)	62 (19.3)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers.

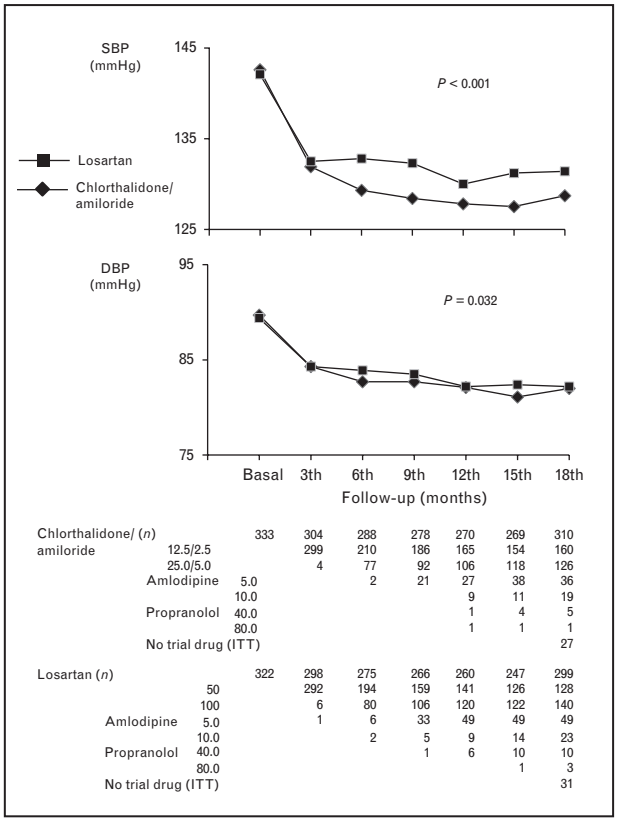

FIGURE 2 SBP and DBP values by study group during follow-up. The number of participants evaluated at each visit and the number who were treated with the higher dosage of their assigned study drug as well as the number that received a prescription for treatment with an open-label drug is shown at each visit. ITT, intention to treat.

least at 12 months (2.2 mmHg). For DBP, the difference was marginally significant at the sixth and 15th month visits. At the end of the trial, 78.8% of patients in the diuretic arm compared with 76.3% of those in the ARB arm had a BP less than 140/90 mmHg ($P = 0.497$).

The largest number of dropouts from the study was noted between the baseline and third month visits (about 8%) with substantial stabilization during subsequent study visits and no overall statistical difference between the two study groups. At the 18th month visit, 27 patients in the diuretic group and 31 in the losartan group who had dropped out of the trial returned for their final study evaluation. More than 80% of those who were evaluated at a regularly scheduled study visit reported that they had taken all or almost all the study pills dispensed at their prior study visit. This information matched with the number of pills that were returned by the participants at each visit. These proportions did not differ by study treatment.

At the final study visit, mean levels of microalbuminuria, glucose, glycosylated hemoglobin, and the proportion of patients with incident microalbuminuria and diabetes were not significantly different by treatment assignment. Serum cholesterol, LDL-cholesterol, triglycerides, and uric acid levels were significantly higher and serum potassium levels were significantly lower in the diuretic arm (Table 2). Electrocardiographic indexes of left ventricular mass declined during follow-up in both the diuretic and the ARB groups but there was no difference in the treatment arm (Table 3).

Adverse events were reported by slightly more than half of the trial participants but there was no significant difference in the treatment arm (Table 4). Self-reported elevated BP tended to be more common in the losartan arm but this difference was not statistically significant. Adverse events, including those that led to discontinuation of the study drugs, were not serious. Thirteen patients complained of sexual dysfunction (impotence, loss of libido, or other complaints), nine in the diuretic group and four in the losartan group ($P = 0.263$).

In analyses stratified by sex, skin color, and age, and in patients with and without obesity, the pattern for BP change in both the treatment arms was similar to that seen in the overall sample. In the subgroup with diabetes (47 in the diuretic arm and 50 in the losartan arm), treatment-related reduction in SBP was similar to that seen in the overall sample, tending to be greater in the diuretic group and approaching a conventional level of statistical significance ($P = 0.053$). The difference in DBP between the two treatment arms in the diabetic patients was not significant ($P = 0.593$). At the 18th month visit, mean (±SD) SBP was 128.4 ± 10.3 for the diabetics in the diuretic arm compared with 133.5 ± 8.0 mmHg in the losartan arm ($P = 0.009$). The corresponding means (SD) for DBP were 80.6 ± 8.2 and 81.8 ± 9.1 mmHg ($P = 0.512$).

Mean (SD) levels of microalbuminuria at the end of the trial tended to be higher in diabetic participants allocated to losartan (28.5 ± 40.4 mg/l) compared with diuretic (16.2 ± 26.7 mg/l) but this difference did not reach a

TABLE 2. Laboratorial outcomes [*N* (%) or mean ± standard deviation]

	Chlorthalidone/amiloride (308)	Losartan (299)	*P*
Serum glucose (mg/dl)	106.3 ± 39.2	102.4 ± 30.6	0.172
Glycosylated hemoglobin (%)	5.9 ± 1.2	5.8 ± 1.2	0.209
Diabetes mellitus (%)	57 (18.4)	48 (16.2)	0.520
Serum cholesterol (mg/dl)	213.0 ± 43.3	201.4 ± 43.6	0.001
LDL-cholesterol (mg/dl)	131.6 ± 42.1	120.6 ± 36.9	0.001
HDL-cholesterol (mg/dl)	51.4 ± 13.8	52.0 ± 14.5	0.574
Triglycerides (mg/dl)	167.7 ± 105.8	151.9 ± 86.4	0.044
Serum potassium (meq/dl)	4.2 ± 0.5	4.5 ± 0.6	<0.001
Serum creatinine (mg/dl)	0.90 ± 0.28	0.90 ± 0.29	0.962
Serum uric acid (mg/dl)	5.9 ± 1.7	5.2 ± 1.4	<0.001
Microalbuminuria (mg/l)	15.5 ± 40.1	16.2 ± 36.4	0.822

TABLE 3. Variation of ECG indexes of left ventricular hypertrophy by treatment group

Index	Group (*n*)	Baseline	Visit 18	*P*
Sokolow–Lyon voltage (mm[a])	Chlorthalidone/amiloride (250)	21.8 ± 6.5	19.9 ± 6.1	0.153
	Losartan (234)	22.0 ± 8.2	20.8 ± 7.3	
Sokolow–Lyon voltage[a] duration (μVms)	Chlorthalidone/amiloride (235)	230.7 ± 89.6	210.2 ± 82.2	0.821
	Losartan (223)	236.8 ± 104.7	215.0 ± 95.1	
Cornell voltage (mm[a])	Chlorthalidone/amiloride (250)	13.5 ± 5.1	13.3 ± 5.0	0.743
	Losartan (234)	13.2 ± 5.2	12.9 ± 5.5	
Cornell voltage[a] duration (μVms)	Chlorthalidone/amiloride (235)	141.5 ± 61.4	138.2 ± 57.2	0.163
	Losartan (223)	141.2 ± 66.0	131.2 ± 61.5	

Patients with valid ECGs at the baseline evaluation and at visit 18; there are fewer patients in the voltage duration indexes because of the imprecision in the measurement of QRS duration. *P*, for interaction time : treatment.
[a]1 mm = 0.1 mV.

conventional level of statistical significance ($P = 0.09$). Following exclusion of those with microalbuminuria at baseline, participants with diabetes who were assigned to losartan tended to have a greater increase in microalbuminuria compared with their counterparts in the diuretic group but this was not statistically significant ($P = 0.10$ for the interaction between drug and treatment in an analysis of variance for repeated measurements). New microalbuminuria was observed in 19.5% of the patients allocated to diuretic and in 27.3% of patients with diabetes allocated to losartan ($P = 0.451$).

DISCUSSION

In this 18-month double-blind RCT of antihypertensive therapy in patients with stage I hypertension, we demonstrated that first-step treatment using a chlorthalidone/amiloride combination pill provided greater reduction in BP compared to treatment with losartan. In addition, more patients treated with losartan received the maximum dosage of their study medication and used more open-label BP-lowering drugs. Levels of blood glucose and glycosylated hemoglobin and new-onset diabetes were not significantly different between the two treatment arms. Serum potassium was lower and serum cholesterol and LDL-cholesterol levels were higher in patients treated with diuretics. Participant reports of adverse events were relatively frequent but rarely resulted in discontinuation of treatment, and most of the reports seemed unrelated to expected pharmacological effects of the drugs. There was no significant difference in the frequency of reported adverse events between the two treatment arms. There was no evidence of superior renal protection in the losartan group. Indeed, in the subgroup of patients with diabetes, there was a trend toward an increased incidence of microalbuminuria at the end of the trial. Electrocardiographic indexes of left ventricular mass indicated improvement to a similar extent with both the treatments.

Our trial was not powered to investigate the effectiveness of the study treatments in prevention of hard endpoints. Nonetheless, it has been demonstrated that the main benefits of antihypertensive treatment are because of lowering of BP *per se* [7,12]. The possibility that other effects of BP-lowering drugs could explain potential advantages of certain drug classes is unlikely for ARB, in face of the results of recent meta-analyses that compared their effectiveness with placebo. The less-intense BP-lowering effect of ARB demonstrated in our trial may explain at least part of the ineffectiveness of these drugs in the prevention of myocardial infarction, cardiovascular events, and all-cause mortality.

Three randomized controlled trials that employed surrogate outcomes to compare the effects of ARB compared with placebo in patients with diabetic nephropathy were

TABLE 4. Self reported adverse events by treatment arm (more than 20 reports)[a]

Number of reports by major groupings	Chlorthalidone/amiloride (333)	Losartan (322)	*P*
Musculoskeletal complaints	68 (20.4)	82 (25.5)	0.137
Digestive complaints	48 (14.1)	37 (11.5)	0.296
Upper respiratory complaints	37 (11.1)	38 (11.8)	0.807
Dizziness	42 (12.6)	29 (9.0)	0.166
Headache	27 (8.1)	34 (10.6)	0.286
Fatigue	34 (10.2)	25 (7.8)	0.279
Urinary/gynecological complaints	18 (5.4)	20 (9.2)	0.739
Blood pressure elevation	12 (3.6)	22 (6.8)	0.078
Edema	10 (3.0)	14 (4.4)	0.409
Psychological complaints	13 (3.9)	11 (3.4)	0.836
Dermatological complaints	12 (3.6)	11 (3.4)	1.00
Polyuria	10 (3.0)	11 (3.4)	0.826
Palpitations	11	9	0.821
Others	85 (25.5)	83 (25.8)	0.987
Total	427	426	NA
Patients that reported at least one adverse event	186 (55.8)	183 (56.8)	0.862

[a]Reported at least once by at least one patient.

the first to provide evidence in favor of ARB as a first-line step therapy in the treatment of hypertension [25–27]. However, the effectiveness of ARB for prevention of major cardiovascular outcomes in patients with hypertension has not been clearly demonstrated. The LIFE trial has been the only study to demonstrate the superiority of losartan against an active comparator, atenolol [28]. This β-blocker, however, may be ineffective as a means to reduce the complications of hypertension [29], at least in elderly patients [30]. In the VALUE trial, the incidence of CHD and stroke was higher in patients randomized to valsartan compared with amlodipine, particularly at the beginning of the study [31]. This trend was attributed to a lower BP-lowering effect of valsartan compared with amlodipine [32]. More recently, ARB treatment has been compared with placebo in a variety of clinical conditions. There has been no report indicating that treatment with ARB proved superior to placebo in the prevention of a number of cardiovascular outcomes [33–39]. Three trials that reported beneficial effects of ARB treatment for nondiabetic renal disease outcomes [40] and CVD morbidity and all-cause mortality [41,42] were retracted because of fraud. Four meta-analyses have reported that treatment with ARB was not superior to placebo in the prevention of all-cause mortality, myocardial infarction, and other major cardiovascular events in various clinical conditions and age ranges [15–18]. It is of note that in patients older than 65 years, ARBs were associated with 3% increased risk of all-cause mortality and 48% increased risk of acute kidney injury in comparison with placebo or other antihypertensive drugs [18]. In a recent meta-analysis, ARB had similar efficacy in the prevention of various cardiovascular outcomes compared with all other classes of BP-lowering agents in patients with type 2 diabetes [43]. However, this finding was entirely based on results from the IDNT [25] and the LIFE [28] trials, with the LIFE trial contributing the majority of the study participants. In another recent meta-analysis that compared the effectiveness of different classes of antihypertensive drug therapy with placebo in patients with hypertension [44], diuretics provided the best protection against cardiovascular events and mortality. This may simply reflect the fact that clinical trials comparisons of diuretic to placebo therapy were conducted at a time when background antihypertensive drug therapy was uncommon and relatively large treatment-related differences in BP were usually achieved. In contrast, newer agents such as the ARBs have been compared with placebo in patients who were already being treated with antihypertensive medication. As a consequence, treatment-related differences in BP seen in these trials have tended to be far less than in the earlier diuretic trials. The authors pointed out that only head-to-head comparison could establish the advantage of any class [44]. In our trial, we demonstrated that at least in terms of BP reduction, diuretics were superior to ARB.

Chlorthalidone was highly effective in the prevention of major cardiovascular events in comparison with placebo in the SHEP trial [45]. In the ALLHAT trial, it was at least as efficacious as lisinopril and amlodipine in the prevention of CHD events and superior to these agents in the prevention of stroke and heart failure [9]. To our knowledge, no trial has directly compared the efficacy of diuretics and ARB as first step drug therapy in the prevention of major CVD outcomes or even their effects on BP and surrogate outcomes during long-term follow-up. Law *et al.* [19] identified 52 trials comparing the BP-lowering effect and other outcomes of ARB with placebo and other drugs. The trials had a median duration of 4 weeks and none compared ARB with a diuretic. If maintained during a lifetime of treatment, the difference in BP noted between the treatment arms in our trial would be expected to result in better CVD protection for those treated with chlorthalidone/amiloride compared with losartan [3,46].

In our trial, serum cholesterol and LDL-cholesterol were higher at the last study visit in the diuretic group, a treatment effect that was also observed during comparison of chlorthalidone with lisinopril in the ALLHAT trial [9]. The magnitude of the difference, however, was greater in our trial. This may have resulted from an adverse effect of amiloride, which we have previously observed in a small trial that compared amiloride with enalapril [22]. Both neutral and adverse effects of amiloride on serum lipid levels have been identified but most of the available reports have been based on studies in which amiloride was used in combination with hydrochlorothiazide. The effects of other potassium-sparing agents, such as spironolactone or triamterene, on serum lipid levels should be explored in future studies. Whatever the explanation for the increase of serum lipids in our trial, it is unlikely that this effect would overwhelm the benefits of the BP-lowering effect of chlorthalidone/amiloride.

Taken together, the well demonstrated effectiveness of chlorthalidone and the uncertain effectiveness of ARB in the prevention of major cardiovascular events, and the greater effectiveness of chlorthalidone in controlling BP in our trial fail to provide credence at this time for the recommendation that ARB drugs should be employed as a first-step drug during treatment of nonblack patients with hypertension [11]. Similarly, the recommendation to employ ARB drugs as an initial option or as a substitute of ACEi in patients with hypertension and microalbuminuria or diabetes is questionable based on the current evidence [12]. Finally, the available data provide little support for the strategy recommended in the NICE guidelines, which starts with ARB (or an ACEi) treatment for management of hypertension in patients younger than 55 years [13].

Among the study limitations is the inability to compare the efficacy of the two study treatments in prevention of major CVD outcomes. Although this is an important issue, the sample size and duration of follow-up needed to achieve this goal was beyond the scope and available funding for the present study. The initial dose of losartan may be low to provide 24-h BP-lowering effect. Nonetheless, this dose was maintained only in patients who had their BP controlled, and was doubled in a high proportion of participants in the following visits. Among the strengths of our study are its double-blind design, concealed allocation, analysis by intention to treat, inclusion of participants from several regions in Brazil, and capacity to investigate cardiac and renal subclinical consequences of high BP. Moreover, it represents the first head-to-head randomized comparisons between the two drugs.

In conclusion, treatment with a combination of chlorthalidone and amiloride, compared with losartan, yielded a greater reduction in BP. There was no evidence of superior renal or cardiac protection by losartan compared with diuretic therapy, particularly in patients with diabetes.

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Conflicts of interest

All of the authors reported they had no conflicts of interest and financial disclosures in regard to the subject of this manuscript.

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Reviewer's Summary Evaluation

Reviewer 1

The main interest in this paper is in being one of the few direct comparisons of a diuretic combination with an ARB. Its main limitation lies in reporting surrogate endpoints only–without any hard endpoints.