ORIGINAL RESEARCH

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Effectiveness of Chlorthalidone Plus Amiloride for the Prevention of Hypertension: The PREVER-Prevention Randomized Clinical Trial

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***Background*—**Prehypertension is associated with higher cardiovascular risk, target organ damage, and incidence of hypertension. The Prevention of Hypertension in Patients with PreHypertension (PREVER-Prevention) trial aimed to evaluate the efficacy and safety of a low-dose diuretic for the prevention of hypertension and end-organ damage.

***Methods and Results*—**This randomized, parallel, double-blind, placebo-controlled trial was conducted in 21 Brazilian academic medical centers. Participants with prehypertension who were aged 30 to 70 years and who did not reach optimal blood pressure after 3 months of lifestyle intervention were randomized to a chlorthalidone/amiloride combination pill or placebo and were evaluated every 3 months during 18 months of treatment. The primary outcome was incidence of hypertension. Development or worsening of microalbuminuria, new-onset diabetes mellitus, and reduction of left ventricular mass were secondary outcomes. Participant characteristics were evenly distributed by trial arms. The incidence of hypertension was significantly lower in 372 study participants allocated to diuretics compared with 358 allocated to placebo (hazard ratio 0.56, 95% CI 0.38–0.82), resulting in a cumulative incidence of 11.7% in the diuretic arm versus 19.5% in the placebo arm (P=0.004). Adverse events; levels of blood glucose, glycosylated hemoglobin, creatinine, and microalbuminuria; and incidence of diabetes mellitus were no different between the 2 arms. Left ventricular mass assessed through Sokolow-Lyon voltage and voltage-duration product decreased to a greater extent in participants allocated to diuretic therapy compared with placebo (P=0.02).

***Conclusions*—**A combination of low-dose chlorthalidone and amiloride effectively reduces the risk of incident hypertension and beneficially affects left ventricular mass in patients with prehypertension.

***Clinical Trial Registration*—**URL: http://www.ClinicalTrials.gov, www.ensaiosclinicos.gov. Unique identifiers: NCT00970931, RBR-74rr6s. **(*J Am Heart Assoc*. 2016;5:e004248 doi: 10.1161/JAHA.116.004248)**

Key Words: amiloride • blood pressure • cardiovascular diseases • chlorthalidone • clinical trials • diuretics • hypertension • left ventricular mass • microalbuminuria • potassium-sparing antihypertensive agents • prehypertension • prevention

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Accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/5/12/e004248/DC1/embed/inline-supplementary-material-1.pdf

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Prehypertension (systolic blood pressure [BP] 120–139 or diastolic BP 80–89 mm Hg) conveys 3 potentially deleterious consequences. First, it substantially increases the risk of developing hypertension.[1,2] In a Brazilian cohort study, 4 of every 5 adults aged 40 to 49 years who had prehypertension were destined to develop hypertension during 10 years of follow-up.[1] Second, patients with prehypertension already have evidence of left ventricular geometric and functional abnormalities[3] and are at higher risk of developing left ventricular hypertrophy.[4] Third, cohort experience provides abundant evidence that, compared with their counterparts with optimal or normal BP levels, adults with prehypertension are at a substantially higher risk of cardiovascular mortality.[5] For these reasons, interventions aimed at lowering BP and preventing cardiovascular disease (CVD) events, target organ damage, and progression to hypertension would seem to be highly desirable for patients with prehypertension.

Clinical trials have already documented the effectiveness of antihypertensive drug therapy in secondary prevention of CVD events in adults with prehypertension.[6] The magnitude of the prevention benefits identified in these trials has been consistent with projections from cohort study experience.[7] Nevertheless, no clinical trial evidence exists to document prevention of CVD events following BP lowering in patients with prehypertension but no history of a clinical CVD event. Given the low absolute risk of a clinical CVD outcome in adults with uncomplicated prehypertension, an event-based trial of antihypertensive treatment in this setting would require a prohibitively large sample size to detect an intervention benefit. Prevention of incident hypertension has already been demonstrated with nonpharmacological[8] and drug treatments[9,10] in patients with prehypertension; however, long-term maintenance of nonpharmacological interventions is difficult.[11] The 2 drug-treatment trials had design limitations,[9–12] studied only patients at the upper limit of prehypertension, and failed to study the effect of treatment on target organ damage.

Our trial was designed to investigate the effectiveness and safety of low-dose diuretic therapy for prevention of hypertension and reduction of target organ damage in adults with prehypertension.

Methods

Study Design

Prevention of Hypertension in Patients with PreHypertension (PREVER-Prevention) was a randomized (concealed), placebo-controlled, double-blind, clinical trial conducted at 21 academic medical centers in Brazil. The study was approved by the ethics committee of the Hospital de Clinicas de Porto Alegre, which is accredited by the Office of Human Research Protections as an institutional review board and by the ethics committee at each medical center. All participants signed an informed consent form prior to participation in the trial. This study was registered at ClinicalTrials.gov (NCT00970931) and ReBEC (Registro Brasileiro de Ensaios Clinicos), and its detailed rationale and methods have been published elsewhere.[13]

Participants

Participants were eligible if they were aged 30 to 70 years, had systolic BP between 120 and 139 mm Hg or diastolic BP between 80 and 89 mm Hg, and were not taking antihypertensive medication. Exclusion criteria included low life expectancy, previous CVD, other indications for the use of a diuretic, study drug intolerance, or pregnancy. Prior to randomization, all study participants were enrolled in a 3-month lifestyle-intervention phase that provided counseling aimed at weight loss, reduction in dietary sodium intake, consumption of a DASH (Dietary Approaches to Stop Hypertension)–type diet, and increased physical activity. Participants whose average BP was still within the prehypertension range after 3 months of lifestyle intervention were randomized to 1 of the 2 treatment groups.

Randomization and Masking

Randomization was performed centrally using a Web-based automated system available on the study's website, with permuted block sizes of 4, 6, 8, or 10, stratified by center. The randomization sequence was generated at the data center using alphanumeric codes and implemented by the study's website independent of the team that enrolled participants and assigned them to the trial groups. After assignment to intervention groups, participants, care providers, and those assessing outcomes remained blinded until the end of the trial.

Interventions

Participants were randomly assigned to receive either a combination pill with chlorthalidone 12.5 mg plus amiloride 2.5 mg (chlorthalidone/amiloride) or placebo at a 1:1 ratio. In the PREVER-Prevention trial, BP-lowering medication was not changed during the experimental phase. Chlorthalidone was chosen because it was widely tested in previous randomized clinical trials and has a longer half-life and greater capacity to lower BP compared with thiazide diuretics such as hydrochlorothiazide.[14] The main adverse effect of chlorthalidone, hypokalemia, can be minimized or avoided by concurrent use of a potassium-sparing agent, such as amiloride.[15] The active and placebo pills were prepared in a certified pharmaceutical laboratory. The study drugs were identical in

size, shape, color, taste, and texture. Follow-up visits were conducted at 3, 6, 9, 12, 15, and 18 months following randomization. Additional visits could be scheduled to assess intercurrent illnesses or adverse effects. Adherence to the treatment was evaluated by self-report and by pill counting.

Outcomes

The primary outcome was incidence of hypertension. Participants with an average of 2 BP measurements ≥140 for systolic BP or ≥90 mm Hg for diastolic BP at the follow-up visits were scheduled for 2 additional BP measurements at a confirmatory visit. Hypertension was diagnosed if the average of all 4 BP measurements was ≥140 mm Hg for systolic BP or ≥90 mm Hg for diastolic BP, according to standardized recommendations.[16,17] Self-reported adverse events, development or worsening of microalbuminuria, changes in left ventricular mass (LVM), and fatal or nonfatal major CVD events were secondary outcomes. Laboratory measurements of fasting plasma glucose, glycosylated hemoglobin, lipid levels, serum electrolyte and uric acid levels, urinary microalbuminuria levels, and 12-lead ECGs were obtained at baseline and at the 18-month visit. All measurements were performed using standardized protocols in core laboratories. Diabetes mellitus was diagnosed when glycosylated hemoglobin was ≥6.5% or plasma fasting glucose was ≥126 mg/dL (7.0 mmol/L). BP was measured twice according to guideline recommendations at 3 clinic visits with a validated automatic electronic device (Microlife BP 3BTO-A; Micromed Biotecnologia Ltda), that captures systolic and diastolic BP by automatically recognizing the beginning and end of cuff oscillation. The average of 6 BP measurements was used to characterize systolic and diastolic BP at baseline and at the end of the trial. Microalbuminuria was determined at the core laboratory by nephelometry. Measurement of LVM was based on ECG recordings using Sokolow-Lyon and Cornell voltage and voltage-duration products.[18,19] Three experienced cardiologists who were blinded to treatment allocation used a semiautomated method to perform the analyses in the ECG core laboratory. Replication of their findings was confirmed by means of a standardized assessment in a subsample. Adverse events were ascertained by self-report of symptoms and responses to a semistructured questionnaire. A committee blinded to treatment assignment adjudicated potential CVD event outcome reports using standardized definitions and procedures.

Quality Control

All study investigators and research staff members were trained and certified in the methods used to implement our trial protocol during regional and individual center meetings. Study data were collected locally using a Web-based system, with central monitoring of the variables collected, periodic reports for review by the participating centers, and a direct check of 15% to 20% of the records in every center. Study performance was monitored electronically, and inconsistencies in the database were reviewed and resolved in a prompt fashion. Monitoring visits onsite were conducted at each center a minimum of 3 times by a study coordinator and twice by the 2 principal investigators (S.C.F. and F.D.F.). Laboratory quality control was supervised by the central laboratory according to standard procedures.

Sample Size

A sample size of 568 participants per group was originally planned with the expectation that this number would provide 85% power to detect a 40% reduction in the incidence of hypertension for participants in the chlorthalidone/amiloride group, assuming a cumulative incidence rate of 14% in the placebo group, with 2-sided α=0.05. The sample size was rounded to 625 per group to compensate for losses during follow-up.

Statistical Analysis

Trial results were analyzed using the intention-to-treat approach. The proportional hazards model for interval-censored failure time data was used to test for statistical significance between the 2 treatment arms and to calculate the hazard ratio and 95% CIs as a measure of the risk of developing hypertension. Plots were used to display the density incidence of hypertension by treatment groups over time. The assumption of proportional hazard risks was tested by using SAS (SAS Institute) to run the supremum test for the proportional hazards assumption, which yielded P=0.488 and was consistent with our proportional hazards assumption.

The comparison of levels of BP among treatment groups at each visit was done using a t test for independent samples, and a random-effects linear model fitted to systolic and diastolic BP 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 systolic and diastolic BP, we included in the model an indicator variable for time (baseline and 3, 6, 9, 12, 15, and 18 months), an interaction term for treatment by time, and the variable treatment. Analyses were repeated with stratification by sex, self-reported skin color,[20,21] age (<50 or ≥50 years), diabetes mellitus, and obesity. Event rates were expressed as the percentage of events by visit and at the end of the trial, taking into account censoring of follow-up data. The comparison of ECG estimates of LVM among the 2 treatment groups was performed by use of a t test for Δ

within and between groups and for laboratory outcomes and Pearson's chi-square test for adverse events at the end of the trial. Participants who abandoned the study for any reason during follow-up were encouraged to attend an 18-month visit for BP measurement and to obtain an ECG recording and laboratory measurements. Statistical analyses were carried out using SPSS version 21.0 (IBM Corp) or SAS version 9.4 using the module SAS/STAT 13.2 user's guide (SAS Institute Inc). Differences with $P<0.05$ were considered statistically significant, without adjustment for multiplicity.

Results

Study Participants

A total of 1433 participants were enrolled in the 3-month lifestyle-intervention phase. Of these, 730 met the criteria for inclusion in the PREVER-Prevention trial at the conclusion of the lifestyle phase and were randomly assigned to treatment with chlorthalidone/amiloride (n=372) or placebo (n=358) (Figure 1). At the 18-month visit, 312 participants in the chlorthalidone/amiloride group and 290 participants in the placebo group were evaluated. During follow-up, 60 participants in the chlorthalidone/amiloride group and 68 in the placebo group discontinued their participation in the study, mostly because of development of hypertension, the main trial outcome. In total, 27 in the intervention group and 43 in the placebo group did not return for the 18-month visit. All others who developed hypertension during follow-up returned for laboratory and ECG evaluations, although most were receiving treatment for hypertension (a conservative bias).

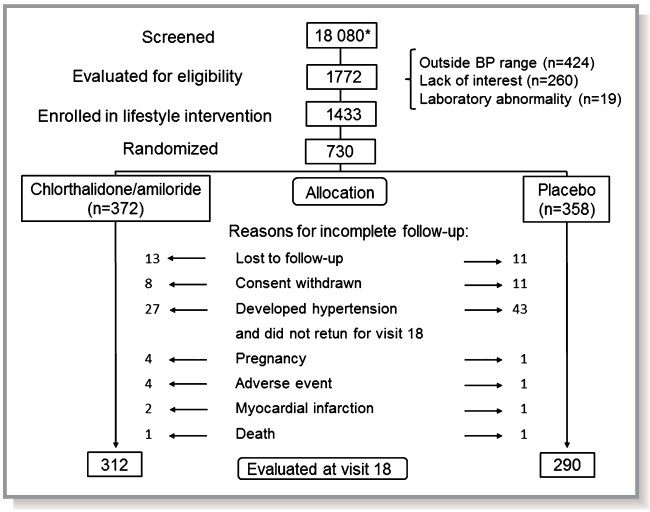

Figure 1. Study flow diagram of the PREVER-Prevention trial, describing selection, randomization, and follow-up process. *Patients were concurrently screened to participate in either the PREVER-Treatment or PREVER-Prevention trial. BP indicates blood pressure.

Two participants in the chlorthalidone/amiloride group and 1 in the placebo group had myocardial infarction during follow-up. There were 2 deaths, 1 in the chlorthalidone/amiloride group from a car accident and 1 in the control group from sudden death.

Baseline characteristics were similar between the 2 groups (Table 1). Participants' mean age was 50.0±10.4 years, 50% were men, 55% were white, and mean systolic and diastolic BP was 127.9±7.3 and 80.5±6.3 mm Hg, respectively. During the trial, self-reported adherence to treatment was similar in both groups, with an average of 84.6% stating they had taken all or almost all of their study pills. Medication adherence estimates based on pill counting were similar, being on average 83.3% for the chlorthalidone/amiloride group and 85.3% for the placebo group.

Incidence of Hypertension

The incidence of hypertension was significantly lower in the chlorthalidone/amiloride group compared with placebo

Table 1. Baseline Characteristics of the PREVER-Prevention Trial Participants

	Intervention (n=372)	Placebo (n=358)
Male	186 (50.0)	179 (50.1)
Age, y	50±10	50±11
White*	195 (52)	206 (58)
Education, years	11±4	11±4
BMI, kg/m^2	29±5	29±5
Obesity (BMI ≥30)	119 (32)	110 (31)
Systolic BP, mm Hg	128±7	128±7
Diastolic BP, mm Hg	81±6	80±6
Potassium, mg/dL	4.6±0.7	4.6±0.6
Uric acid, mg/dL	5±1	5±1
Cholesterol, mg/dL	193±37	193±41
LDL-C, mg/dL	117±33	120±34
HDL-C, mg/dL	47±13	46±13
Triglycerides, mg/dL	145±87	143±99
Creatinine, mg/dL	0.8±0.2	0.8±0.2
Microalbuminuria, μg/24 h	6.3±5.9	7.0±6.3
Diabetes mellitus (%)†	30 (8)	29 (8)
Current smokers	28 (8)	37 (10)
Current alcoholic consumption	227 (61)	206 (58)

Data are shown as n (%) or mean±SD. BMI indicates body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Self-reported and categorized as white or nonwhite. Previous physician's diagnosis, use of antidiabetics, abnormal fasting glucose, or glycosilate hemoglobin at the baseline.
†Previous physician's diagnosis, use of antidiabetics, abnormal fasting glucose, or glycosilate hemoglobin at the baseline.

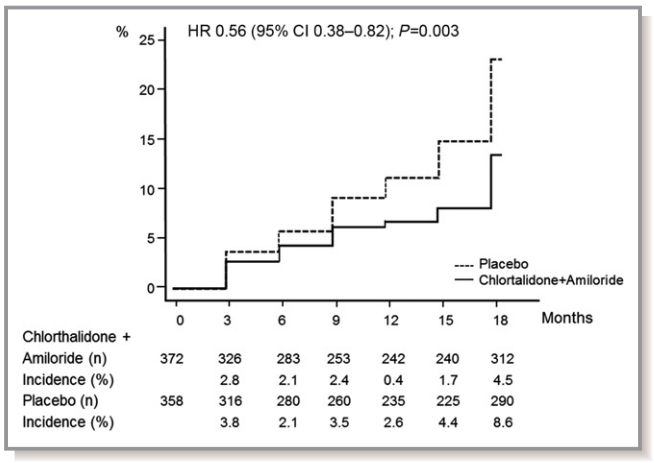

Figure 2. Incidence of hypertension according to treatment group during follow-up. HR indicates hazard ratio.

(hazard ratio 0.56, 95% CI 0.38–0.82; *P*=0.003), with an apparent progressively larger difference in incident hypertension between the 2 treatment groups over time (Figure 2). The cumulative incidence of hypertension was 11.7% in the diuretic group compared with 19.5% in the placebo group (*P*=0.004).

BP During Follow-up

The temporal pattern for mean systolic and diastolic BP is displayed in Figure 3. Systolic BP was significantly lower in the chlorthalidone/amiloride group compared with placebo at every follow-up visit, and diastolic BP was significantly lower at the 3- and 12-month visits (Table 2). Overall, the differences were highly significant both for systolic BP (*P*=0.001) and diastolic BP (*P*=0.04) (Figure 3). There was a trend of greater reduction in pulse pressure in the diuretic arm (mean 45.3, 95% CI 44.6–46.1) compared with the placebo arm (mean 46.3, 95% CI 45.6–47.1; *P*=0.06).

ECG Changes in LVM

Both Sokolow-Lyon estimates identified a significant treatment-related reduction in LVM in the chlorthalidone/amiloride group (21.8±7.5 to 20.7±7.1 mm) but no corresponding change in the placebo group (21.5±7.4 to 21.5±7.2 mm), with a statistically significant (*P*=0.02) difference in LVM between the 2 treatment groups at 18 months (Table 3). Although the change in Sokolow-Lyon voltage (in mm) was small, the difference across groups for Sokolow-Lyon voltage

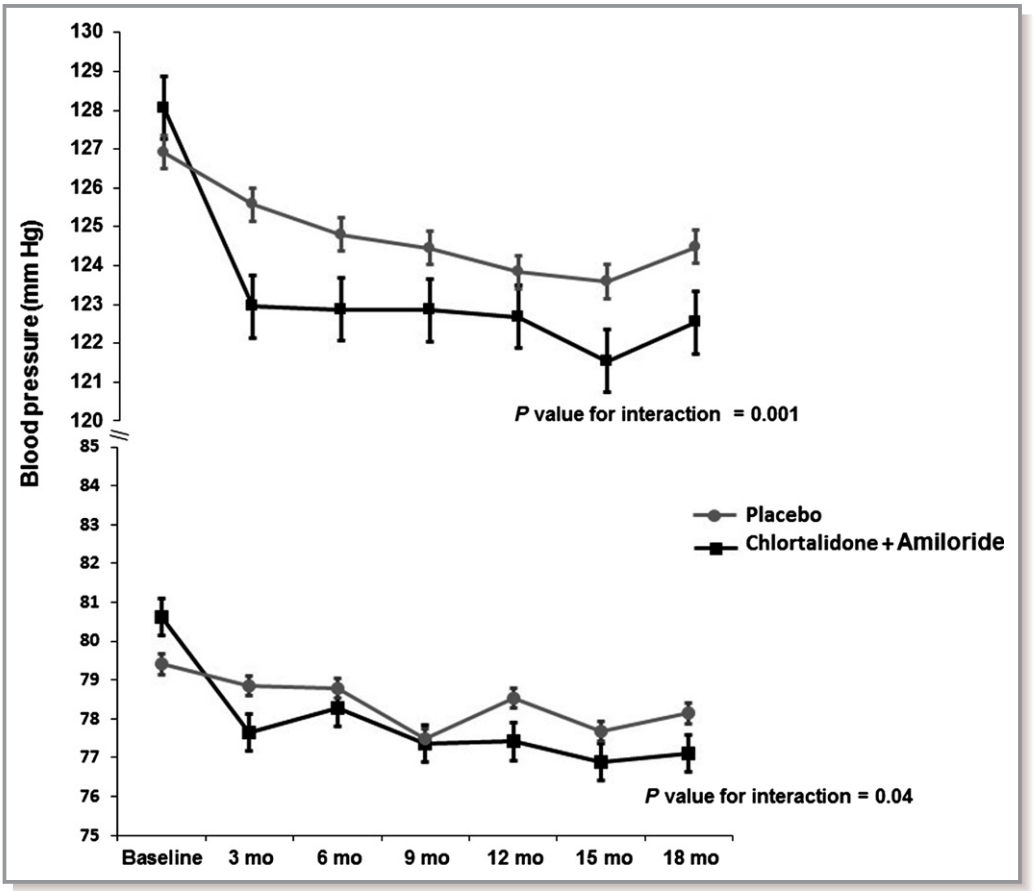

Figure 3. Blood pressure according to treatment group during follow-up.

Table 2. Blood Pressure Evaluated at Each Visit Until the Development of Hypertension

Visit	No. of Patients, Chlorthalidone+Amiloride/ Placebo	Blood Pressure (mm Hg)	Chlorthalidone+Amiloride, Mean±SD	Placebo, Mean±SD	*P* Value*
Baseline	372/358	Systolic	127.9±7.3	126.6±9.0	0.80
		Diastolic	80.6±6.4	80.4±6.2	0.67
3 mo	326/316	Systolic	123.8±8.5	126.6±9.0	<0.001
		Diastolic	78.6±6.7	79.9±6.9	0.01
6 mo	283/280	Systolic	123.8±8.2	125.8±8.0	0.004
		Diastolic	79.0±6.5	79.6±6.8	0.36
9 mo	253/260	Systolic	123.3±8.4	125.6±8.8	0.003
		Diastolic	78.4±6.6	79.3±7.4	0.13
12 mo	242/235	Systolic	122.9±8.6	124.7±8.8	0.02
		Diastolic	77.8±6.6	79.1±6.7	0.03
15 mo	240/225	Systolic	122.2±8.5	124.5±9.1	0.005
		Diastolic	77.5±6.4	78.3±7.4	0.19
18 mo	312/290	Systolic	123.5±9.9	125.6±10.2	0.01
		Diastolic	78.0±7.8	78.4±7.8	0.48

*Analysis using a *t* test for independent samples at each time point.

duration product was higher. There was a similar nonsignificant trend for Cornell voltage duration product estimates of LVM.

Microalbuminuria and Other Laboratory Outcomes

At the end of the trial, the mean level of microalbuminuria in the 2 treatment groups was no different (11.1±17.5 versus 10.6±16.1 μg/24 h in the diuretic and placebo groups, respectively). Table 4 shows the baseline to last visit variation for laboratory outcomes. The variations in low-density lipoprotein cholesterol, potassium, and uric acid were significantly higher in the active arm compared with the control arm, and the variation in total cholesterol presented a trend of significance. Overall, 5.5% of the participants in the intervention group (n=308) and 3.3% in the placebo group (n=305) developed diabetes mellitus

Table 3. Left Ventricular Mass Detected by ECG Indexes According to Treatment Groups

ECG Index and Treatment Group	n	Baseline	18-Month Visit	Mean Difference From Baseline to 18-Month Visit (95% CI)	Mean Difference Between Treatment Groups (95% CI)	*P* Value*
Sokolow-Lyon voltage, mm†						
Chlorthalidone/amiloride	251	21.8±7.5	20.7±7.1	1.04 (0.45–1.63)	1.01 (0.13–1.88)	0.02
Placebo	257	21.5±7.4	21.5±7.2	0.03 (−0.61 to 0.68)		
Sokolow-Lyon voltage duration product, μVms						
Chlorthalidone/amiloride	246	229.0±102.7	213.3±83.6	15.44 (5.65–25.24)	16.89 (3.11–30.62)	0.02
Placebo	253	223.0±98.6	224.4±94.4	−1.43 (−11.08 to 8.23)		
Cornell voltage, mm†						
Chlorthalidone/amiloride	252	1.25±0.53	1.21±0.50	0.04 (−0.01 to 0.09)	0.47 (−0.20 to 1.15)	0.17
Placebo	259	1.21±0.50	1.22±0.50	−0.01 (−0.05 to 0.04)		
Cornell voltage duration product, μVms						
Chlorthalidone/amiloride	247	129.5±65.5	122.8±56.3	6.79 (−0.27 to 13.84)	9.14 (−0.77 to 19.05)	0.07
Placebo	254	125.3±63.7	127.7±69.0	−2.35 (−9.31 to 4.60)		

*Analysis using a *t* test for independent samples for the between-group difference.
†1 mm=0.1 mV for patients with valid ECGs at the baseline evaluation and at visit 18.

Table 4. Laboratory Outcomes According to Treatment Groups

	n	Baseline, Mean±SD	18-Month Visit, Mean±SD	Mean Difference From 18-Month Visit to Baseline (95% CI)	Mean Difference Between Treatment Groups (95% CI)	*P* Value*
Glucose, mg/dL						
Chlorthalidone/amiloride	332	94.9±22.16	97.4±21.6	2.50 (0.50 4.50)	1.53 (−1.18 to 4.24)	0.27
Placebo	328	93.9±22.03	94.9±22.9	0.97 (−0.86 to 2.80)		
Glycosilate hemoglobin (%)						
Chlorthalidone/amiloride	328	5.5±0.9	5.7±1.1	0.18 (0.09–0.27)	0.10 (−0.022 to 0.22)	0.11
Placebo	320	5.4±0.8	5.5±0.9	0.08 (0.004 to −0.16)		
Cholesterol, mg/dL						
Chlorthalidone/amiloride	336	193.0±38.2	209.8±46.4	16.74 (12.70–20.78)	4.98 (−0.73 to 10.69)	0.09
Placebo	329	192.0±41.7	203.8±43.3	11.77 (7.72–15.81)		
LDL-C, mg/dL						
Chlorthalidone/amiloride	330	117.4±33.9	130.3±43.6	12.88 (8.67–17.08)	8.10 (2.76–13.43)	0.003
Placebo	322	119.9±34.1	124.7±37.1	4.78 (1.51–8.05)		
HDL-C, mg/dL						
Chlorthalidone/amiloride	333	47.6±13.1	51.4±14.7	3.84 (2.73–4.95)	1.14 (−0.41 to 2.68)	0.15
Placebo	328	46.3±12.3	49.0±12.6	2.70 (1.62–3.78)		
Triglycerides, mg/dL						
Chlorthalidone/amiloride	334	144.9±82.3	151.7±89.7	7.78 (0.15–15.41)	−3.63 (−15.40 to 8.14)	0. 5
Placebo	328	139.3±89.0	150.0±90.0	11.41 (2.39–20.43)		
Potassium, mg/dL						
Chlorthalidone/amiloride	332	4.6±0.7	4.4±0.5	−0.23 (−0.32 to −0.15)	−0.15 (−0.27 to −0.02)	0.02
Placebo	321	4.6±0.6	4.5±0.6	−0.09 (−0.18 to 0.003)		
Creatinine, mg/dL						
Chlorthalidone/amiloride	337	0.8±0.2	0.9±0.2	0.095 (0.08–0.11)	0.002 (−0.05 to 0.05)	0.9
Placebo	329	0.8±0.2	0.9±0.4	0.093 (0.05–0.14)		
Uric acid, mg/dL						
Chlorthalidone/amiloride	336	5.3±1.4	5.6±1.4	0.34 (0.22–0.45)	0.27 (0.12–0.42)	<0.001
Placebo	329	5.2±1.4	5.3±1.3	0.07 (0.03–0.17)		
Microalbuminuria, μg/24 h						
Chlorthalidone/amiloride	334	6.3±6.1	11.1±17.5	4.81 (3.0–6.6)	1.15 (−1.38 to 3.68)	0.37
Placebo	328	6.9±6.3	10.6±16.1	3.66 (1.90–5.43)		

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Analysis using t-test for independent samples.

(*P*=0.18). The incidence of new albuminuria in patients free of albuminuria (<25 μg/24 h) was similar among participants allocated to placebo (9.8%) and active treatment (7.7%; *P*=0.35).

Safety

There was no statistically significant difference in overall or individual self-reported adverse events between the 2 treatment groups (Table 5). Musculoskeletal complaints, dizziness, and headache were the adverse events more frequently cited by participants in both arms. Sexual dysfunction was reported by 2 (0.5%) participants allocated to diuretic and 7 (2.0%) allocated to placebo (*P*=0.08). Four participants allocated to the chlorthalidone/amiloride group discontinued their participation in the study because of an adverse event (Figure 1). Of these, 1 complained of itching, 2 reported weakness and dizziness, and 1 had an abdominal rash. In the

Table 5. Adverse Events According to Treatment Groups During the Trial

Adverse Events*	Chlorthalidone/ Amiloride (n=372)	Placebo (n=358)	*P* Value†
Musculoskeletal complaints	32 (8.6)	30 (8.4)	0.9
Dizziness	33 (8.9)	25 (7.0)	0.4
Headache	19 (5.1)	27 (7.6)	0.17
Gastroesophagic reflux symptoms	20 (5.4)	16 (4.5)	0.6
Other digestive complaints	13 (3.5)	18 (5.0)	0.3
Sleep complaints	13 (3.5)	13 (3.6)	0.9
Polyuria	16 (4.3)	8 (2.2)	0.12
Fatigue	9 (2.4)	14 (3.9)	0.2
Palpitations	6 (1.6)	10 (2.8)	0.3
Torax pain or discomfort	6 (1.6)	9 (2.5)	0.4
Eyes complains	7 (1.9)	5 (1.4)	0.6
Syncope	6 (1.6)	4 (1.1)	0.6
Sexual dysfunction (impotence, loss of libido or others)	2 (0.5)	7 (2.0)	0.08
Cramps	7 (1.9)	2 (0.6)	0.11
Vascular complaints	5 (1.3)	4 (1.1)	0.8
Lithiasis	2 (0.5)	7 (2.0)	0.08
Dermatological complaints	7 (1.9)	2 (0.6)	0.11
"High BP"	2 (0.5)	4 (1.1)	0.4
"Low BP"	3 (0.8)	2 (0.6)	0.7
Psychological complaints	4 (1.1)	9 (2.5)	0.14
Other adverse events	59 (15.9)	50 (14.0)	0.5
At least 1 adverse event	142 (38.2)	136 (38.1)	1.0

*Reported at least once by at least 1 patient.
†Analysis using a *t* test for independent samples.
BP indicates blood pressure.

placebo group, 1 participant who complained of weakness and dizziness abandoned the study.

Stratified Analyses

Figure 4 displays the risk of incident hypertension by baseline categories of age, sex, skin color, BP, and presence or absence of diabetes mellitus. The only category that yielded a significant treatment interaction was sex, with an apparently greater benefit of chlorthalidone/amiloride treatment for women than men. Diabetes mellitus and obesity were more prevalent in women compared with men, but adjustment for these conditions did not modify the estimate substantially. Despite the absence of a significant interaction, the risk ratios for incident hypertension decreased in a progressive manner with increasing decades of age: 30 to 39 years, 0.89 (95% CI 0.41–1.97); 40 to 49 years, 0.62 (95% CI 0.31–1.23); 50 to 59 years, 0.48 (95% CI 0.23–0.99); 60 to 70 years, 0.40 (95% CI 0.15–1.04). Incidence of hypertension tended to be lower in participants with diabetes mellitus at baseline, but the interaction term did not meet a conventional level of significance.

Discussion

In this randomized, double-blind, placebo-controlled, clinical trial, treatment using low doses of a thiazide-type diuretic combined with a potassium-sparing agent prevented the incidence of hypertension by almost 50% in patients with prehypertension. Moreover, the intervention appeared to be safe and resulted in a small but nominally significant reduction in LVM, as estimated by ECG. The incidence of new-onset hypertension was reduced by ≈4% year, corresponding to a number needed to treat of ≈25. During 18 months of follow-up, BP reduction was modest and would be of insufficient magnitude to demonstrate a significant reduction in clinical complications over a 5- to 10-year period of follow-up, even in a study with a very large sample size. Nonetheless, the consequences of hypertension occur over several decades. If maintained, effects of the size noted in our trial would likely place many patients in a different track for increasing BP with age, promoting lower age-related levels of BP, prevention of CVD outcomes, and potentially avoiding of the need for high doses of antihypertensive medications later in life.

Two previous randomized clinical trials have tested the efficacy of drug treatment in prevention of hypertension.[9,10] In the Trial of Preventing Hypertension (TROPHY) study,[9] 2 years of treatment with candesartan at a dose of 16 mg/day reduced the incidence of hypertension by 66% compared with placebo. This trial was similar to ours in its sample size (n=772) and its use of blinding among participants, research team, physicians, and cardiologists. The 2 trials, however, had several important differences. First, recruitment in the TROPHY study was restricted to participants with BP in the upper end of the range for definition of prehypertension (systolic BP between 130 and 139 mm Hg or diastolic BP between 85 and 89 mm Hg),[9] whereas we enrolled participants who met the generally recommended BP requirements for diagnosis of prehypertension (systolic BP between 120 and 139 mm Hg or diastolic BP between 80 and 89 mm Hg). Consequently, mean baseline systolic and diastolic BP values were about 6 and 5 mm Hg higher, respectively, in the TROPHY study. Another important difference between the 2 trials was the choice of dosage for active treatment. We chose to use low doses of chlorthalidone and amiloride (12.5 and 2.5 mg/day, respectively), whereas the TROPHY investigators used the standard dose of candesartan (16 mg/day). Consequently, the difference in BP between the treatment groups

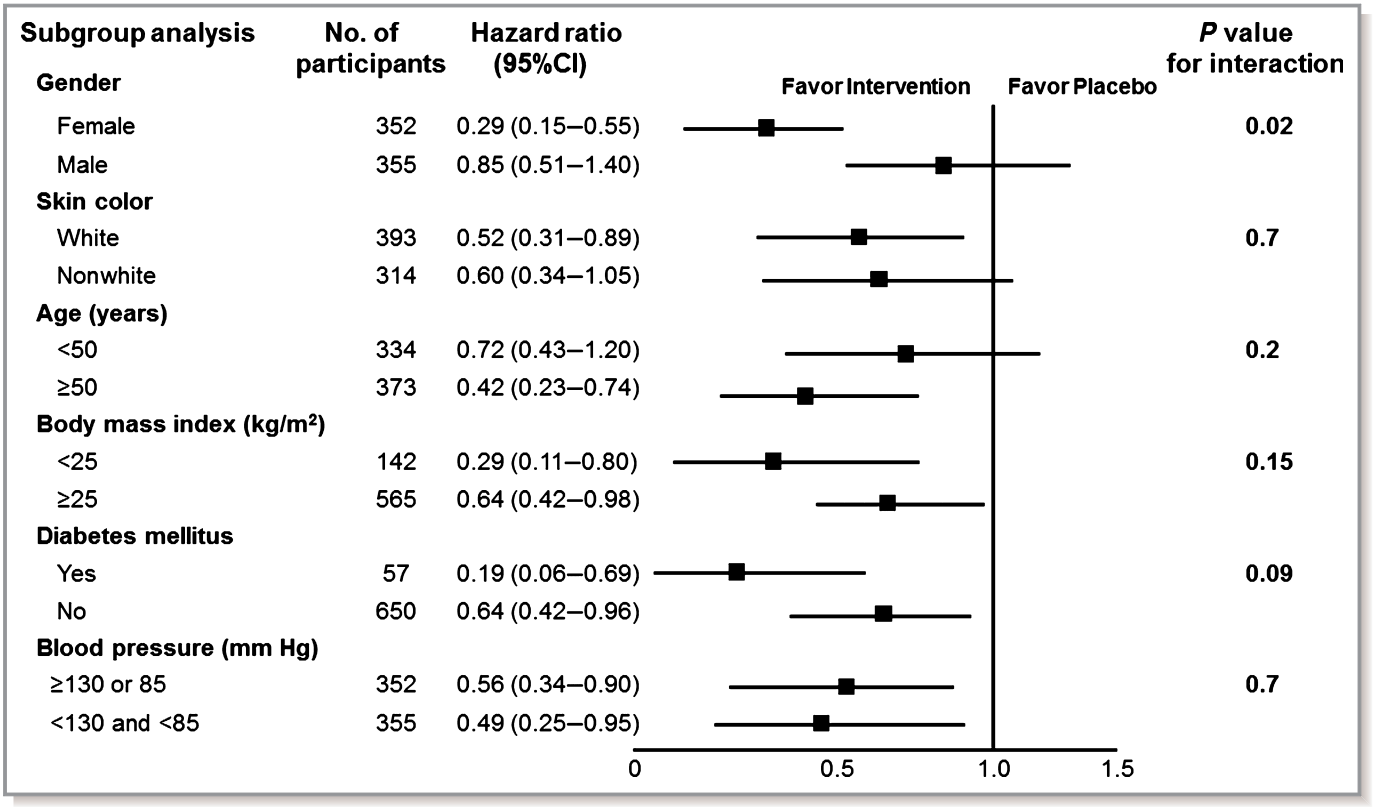

Figure 4. Hazard ratio (95% CI) for hypertension in participants stratified by clinical and demographic characteristics.

appears to have been ≈2 to 3 times larger in the TROPHY study. Finally, the criteria for detection of incident hypertension during follow-up in the TROPHY study were less stringent than generally recommended.[16,17] A modeling investigation reported that use of the TROPHY diagnostic criteria would lead to spurious recognition of hypertension in 78% of those studied during 18 clinic observations (the number of follow-up visits in TROPHY).[22] In contrast, reanalysis of the TROPHY study using the criteria for diagnosis of hypertension recommended in hypertension guideline documents yielded an estimate for reduction in relative risk of incident hypertension (0.32, 95% CI 0.24–0.42) similar to the original report.[23]

In the Prevention of hypertension with the angiotensin converting enzyme inhibitor ramipril in patients with high-normal blood pressure (PHARAO) study,[10] 1008 participants with mean systolic BP between 130 and 139 mm Hg or diastolic BP between 85 and 89 mm Hg were randomized to 3 years of open-label treatment with ramipril 5 mg daily or no treatment. The relative risk reduction for incidence of hypertension during follow-up was 34% (hazard ratio 0.66, 95% CI 0.53–0.81). Cough was more frequent in the ramipril group (4.8% versus 0.4%). As was the case for the TROPHY study, the participants in PHARAO had baseline BPs at the upper end of the definition for prehypertension. A limitation of the PHARAO study was the use of an open design, although BP was measured with an automated device.

The findings of the PREVER-Prevention, TROPHY, and PHARAO trials are consistent. Our study documents the value of low-dose antihypertensive drug therapy for prevention of hypertension. It also demonstrates a similar treatment-related hypertension-prevention benefit throughout the entire range of prehypertension BP levels. It is worth noting that our trial and the SPRINT study[24] addressed the same issue (prevention of CVD) at opposite ends of the BP distribution. In SPRINT, an average of 3 drugs were used to lower systolic BP from hypertensive to optimal levels, and this yielded a very impressive decrease in "hard" CVD outcomes. In our study (without hard end points), we demonstrated that merely using a half dose of the first drug used in SPRINT (chlorthalidone) prevented the expected increase in BP to hypertensive levels in a high proportion of patients studied.

To our knowledge, the PREVER-Prevention trial is the first study to demonstrate a reduction in LVM following low-dose antihypertensive drug therapy in adults with prehypertension. In the TOHMS trial, which enrolled participants with higher levels of BP than those used in PREVER (baseline diastolic BP 90–99 mm Hg in adults with untreated hypertension or 85–99 mm Hg over 3 visits following withdrawal of antihypertensive medication), the incidence of resting ECG abnormalities was lesser in patients randomized to antihypertensive medication compared with placebo.[19] The reduction in LVM evaluated by echocardiogram was greater in those randomized to

chlorthalidone (15 mg/day) compared with their counterparts randomized to acebutolol (400 mg/day), doxazosin (2 mg/day), amlodipine (5 mg/day), or enalapril (5 mg/day).[25,26] Left ventricular hypertrophy detected by ECG has long been recognized as a CVD risk independent of BP levels and hypertension, a finding that has been confirmed.[27,28]

Diuretics may be particularly efficacious in prehypertension because excess consumption of sodium is likely to initiate the pathophysiological changes that characterize this stage in the natural history of hypertension. A common feature of isolated populations that experience little, if any, age-related increase in BP is their modest consumption of dietary sodium.[29] The age-related increase in BP commonly seen in most societies is thought to represent a pathophysiological response that facilitates renal excretion of excessively high levels of dietary sodium consumption. Over time, high BP is thought to result in a progressive loss of renal glomeruli and hypertrophy of the renal arterioles, which leads to a requirement for even higher levels of BP to facilitate natriuresis and maintenance of a normal level of intravascular volume. This recurring pathophysiological cycle eventually results in left ventricular and arteriolar hypertrophy and other manifestations of subclinical disease.[30] After a prolonged period of high peripheral resistance and increased levels of diastolic BP, the larger arterial vessels become stiffer, with a consequent rise of systolic BP levels. This deleterious pattern of progressive rise in BP with aging may be aborted in the early stages of its natural history by adoption of a diet with reduced sodium intake or by natriuresis, which can be accomplished by administration of a diuretic at low dose. The effect on systolic pulse pressure may lead to a decrease in central BP. This would be another mechanism for cardiovascular protection, reducing the increase in LVM in the group treated with diuretics. This possibility would have to be explored in future studies because we did not measure central BP.

Dietary change represents the optimal approach, but achieving and maintaining a meaningful reduction in dietary sodium through lifestyle change has proven to be very difficult.[31] While continuing to promote adoption of a healthy diet, use of diuretics at low dose may be a more effective means of achieving natriuresis and interrupting the dangerous cycle of BP response to excessive consumption of sodium.

In our study, the incidence of hypertension was similar to that described in a cohort study conducted previously in Porto Alegre, Brazil.[1] The curves for incidence of hypertension in the 2 treatment groups started to diverge at an early stage, and the difference between the 2 treatment arms became increasingly prominent over time. This suggests that continued administration of a low-dose diuretic could reverse the pathophysiology that underpins typical age-related increases in BP. Likewise, the beneficial effects on LVM that we noted during diuretic therapy suggest that these deleterious effects of high normal BP can also be prevented.[2]

The interaction between treatment and sex was unexpected, and it could not be readily explained by adjustment or by differences in adherence to treatment. It may represent a chance finding. In clinical event trials, the efficacy of chlorthalidone treatment has not been influenced by sex.[32,33] The nonsignificant trend for greater efficacy in patients with diabetes mellitus could have resulted from chance or could be explained by the higher risk of developing hypertension in those who already have diabetes mellitus, which may be caused by loss of glomeruli and insulin-induced sodium retention.

At the end of our study, levels of low-density lipoprotein cholesterol and uric acid were higher in the participants treated with the chlorthalidone/amiloride combination pill, findings that have been noted frequently during diuretic therapy.[34] In comparison with placebo treatment, levels of high-density lipoprotein cholesterol were also higher in the participants treated with diuretics, whereas potassium was slightly lower. The long-term consequences of these differences are uncertain, but even if the consequences are deleterious, they are unlikely to exceed the benefit of preventing incident hypertension. In our trial, participants treated with diuretic did not experience a significant increase in blood glucose or glycosylated hemoglobin levels. An increased incidence of biochemical diabetes has been noted during therapy with higher levels of chlorthalidone,[32,33] but the biological implications of this type of diabetes appears to be benign in contrast to the high risk of CVD in persons with obesity-related diabetes mellitus.[34]

Study Limitations

A limitation of our study was its sample size. Because of resource limitations, it was not possible to enroll as many participants as originally planned. The trial was sufficiently large to allow for a satisfactory and highly significant test of our main hypothesis (intervention-related prevention of hypertension). Nonetheless, there was less satisfactory power to assess the effect of the intervention on our secondary outcomes. In addition, we had several secondary outcomes, so the significant difference in LVM could have resulted from chance due to multiple hypothesis testing. Another limitation of our trial was the absence of out-of-office BP measurements. Because of this, we were unable to assess the effect of our treatment on nighttime BP and the potential role of “white coat” and masked hypertension.

Despite these limitations, our study had many important strengths including use of a concealed approach to randomization, a double-blind design, analysis by intention to treat, rigorous attention to quality control, blinded adjudication of study outcomes, and a diverse sample that included

participants from 21 academic centers distributed across 10 states in Brazil.

In conclusion, use of a fixed combination of low-dose chlorthalidone and amiloride produced a substantial and highly significant reduction in the incidence of hypertension and a reduction in LVM in patients with prehypertension. The use of low-dose diuretics in patients with prehypertension may be an effective option to reduce the burden of hypertension and its cardiovascular consequences.

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Disclosures

None.

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Effectiveness of Chlorthalidone Plus Amiloride for the Prevention of Hypertension: The PREVER–Prevention Randomized Clinical Trial

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