Original Article

Effectiveness of low-dose diuretics for blood pressure reduction to optimal values in prehypertension: a randomized clinical trial

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Background: To determine the effectiveness of low-dose diuretic therapy to achieve an optimal level of blood pressure (BP) in adults with prehypertension.

Methods: The PREVER-prevention trial was a randomized, parallel, double-blinded, placebo-controlled trial, with 18 months of follow-up, conducted at 21 academic medical centers in Brazil. Of 1772 individuals evaluated for eligibility, 730 volunteers with prehypertension who were aged 30–70 years, and who did not reach optimal blood pressure after 3 months of lifestyle intervention, were randomized to a fixed association of chlorthalidone 12.5 mg and amiloride 2.5 mg or placebo once a day. The main outcomes were the percentage of participants who achieved an optimal level of BP.

Results: A total of 372 participants were randomly allocated to diuretics and 358 to placebo. After 18 months of treatment, optimal BP was noted in 25.6% of the diuretic group and 19.3% in the placebo group ($P < 0.05$). The mean net reduction in SBP and DBP for the diuretic group compared with placebo was 2.8 mmHg (95% CI 1.1 to 4.5) and 1.1 mmHg (95% CI −0.09 to 2.4), respectively. Most participants in the active treatment group (74.5%) and in the placebo group (80.7%) continued to have BP in the prehypertension range or progressed to hypertension.

Conclusion: Low-dose diuretic therapy increased the probability of individuals with prehypertension to achieve optimal BP but most of those treated continued to have a BP in the prehypertension range or progressed to having overt hypertension.

Keywords: chlorthalidone and amiloride, clinical trials, hypertension, optimal blood pressure, prehypertension

Abbreviations: BP, blood pressure; CVD, cardiovascular disease

INTRODUCTION

Epidemiological studies demonstrate a progressively higher risk of cardiovascular disease (CVD) with increasing levels of SBP and DBP, starting at SBP/DBP values as low as 115/75 mmHg [1,2]. A variety of nonpharmacological interventions, including lifestyle modifications aimed at changing dietary intake and physical activity, are effective in lowering BP [3] but the benefits are hard to maintain during long-term follow-up [4,5]. Antihypertensive drug therapy not only lowers BP but has been repeatedly shown to reduce the risk of CVD [6]. Some opinion leaders believe that the benefits of antihypertensive drug therapy remain unproven for adults with a SBP/DBP lower than 140/90 mmHg [7–9]. Others have

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expressed concern that intensive lowering of BP in patients with hypertension could be harmful because of the J-curve phenomenon [10,11]. However, In the Systolic Blood Pressure Intervention Trial (SPRINT), treatment to a SBP target of 120 mmHg compared with 140 mmHg resulted in a substantial reduction in CVD events and all-cause mortality in adults with hypertension and an increased risk of CVD [12]. The benefits were also noted in those at least 75 years at baseline with the most frailty or slowest gait speed [13]. Pooling estimates in several large meta-analyses (with or without the SPRINT findings) [14–16], as well as BP-lowering in nonhypertensive adults with CVD [17,18], suggest that more intensive treatment to a target of 130 mmHg or less or 120 mmHg is beneficial in adults at high risk for CVD. Canadian [19] and Australian [20] BP management guidelines have incorporated a recommendation for intensive BP reduction in selected patients at high risk for CVD.

In addition to being a risk factor for incidence of hypertension [21,22], prehypertension (SBP 120–139 mmHg or DBP 80–89 mmHg) is also a risk for target-organ damage [23–25] and for CVD [1,2]. Two randomized controlled trials have demonstrated that low-dose antihypertensive drug therapy compared with placebo reduces the incidence of hypertension in adults with a baseline BP in the upper range of prehypertension [26,27]. Recently, the PREVER-prevention trial demonstrated that treatment with a low dose of chlorthalidone in combination with a low dose of the potassium-sparing agent amiloride (chlorthalidone–amiloride), compared with placebo, not only reduced the incidence of hypertension in patients with BP within the full range of prehypertension by 44% but significantly improved ECG-estimated left ventricular mass [28].

The rationale for lowering BP to less than 120/80 mmHg is, therefore, coherent and consistent. As far we know, we report the findings of the first clinical trial of drug treatment to optimize BP of individuals with prehypertension without CVD who did not respond adequately to efforts aimed at lifestyle modification.

METHODS

Details of the PREVER-prevention trial have been reported elsewhere [28,29]. The study was a randomized, placebo-controlled, double-blinded clinical trial, conducted at 21 academic medical centers in Brazil. The trial was approved by the Ethics Committee of the participating clinical centers and the study was registered at the clinicaltrials.gov site (NCT00970931).

Participants with prehypertension who were not taking antihypertensive medication were enrolled in the trial. Prior to randomization, study participants received a 3-month lifestyle change intervention, which provided dietary counseling and a recommendation to increase physical activity. Volunteers whose average BP remained within the prehypertension range were randomized to a combination of once daily low-dose (12.5 mg) chlorthalidone with amiloride (2.5 mg) or placebo, in a 1 : 1 ratio. Follow-up visits were conducted at 3, 6, 9, 12, 15, and 18 months following randomization.

The primary goals of the trial were to investigate the effectiveness of a low-dose diuretic for prevention of hypertension, to evaluate the safety of the intervention, and to examine its effects on target-organ damage. In this manuscript, we report the percentage of participants allocated to the active treatment and placebo who achieved an optimal level of BP (<120/80 mmHg) during treatment.

BP was measured with a validated automatic electronic device (Microlife BP 3BTO-A; Microlife Corporation, Timóteo, MG, Brazil). An average of six BP measurements (two readings at each of three visits) was used to characterize SBP and DBP at baseline and an average of four BP measurements (two readings at each of two visits) was employed at the end of the trial.

Participants who had abandoned the study for any reason during the follow-up were encouraged to attend their 18th month visit for measurement of BP, recording of a 12-lead ECG, and laboratory measurements.

There was no a priori sample size calculation for this post hoc analysis. A Generalized Estimating Equation (GEE) model was employed to test for the proportion of participants who reached optimal blood pressure by treatment groups during the follow-up, using a binomial probability distribution with an exchangeable correlation matrix structure. Relative risk for optimal blood pressure at 18 months of follow-up was calculated using Poisson regression models with a robust estimator and test of interaction between the intervention groups and each of the prognostic factors, such as sex, self-reported skin color, age (below or 50 years and over), diabetes mellitus, obesity, and BP within the higher and lower range for prehypertension. The Poisson model fit was verified through the goodness of fit (P values higher than 0.99 for all tests).

BP distribution curves by treatment group at the final visit were graphically fitted and the means were compared by means of a Student's t-test for independent samples. Statistical analyses were carried out using SPSS, version 21.0, (SPSS, Armonk, New York, USA).

RESULTS

The number of individuals screened for the trial, reasons for exclusion and the proportion of those who responded to the lifestyle recommendations were presented in the main trial report [28]. Table 1 displays a selected group of baseline demographic, clinical and laboratory characteristics in the two treatment groups and demonstrates that the measurements were similar in the 372 adults randomized to the chlorthalidone and amiloride combination and the 358 randomized to placebo. During follow-up, 60 participants in the chlorthalidone and amiloride group and 68 in the placebo group discontinued their participation in the study, mostly ($n = 70$) because of development of hypertension, the main trial outcome.

Figure 1 shows the percentage of participants in the two trial arms, who had an optimal BP at each follow-up visit. Most of the reduction in BP to an optimal value occurred between study entry and the first visit. In subsequent visits, the percentage of patients with an optimal BP remained relatively stable. At the final visit (18th months), 92 (25.6%) participants in the active treatment group and 67 (19.3%) participants in the placebo group had an optimal BP ($P < 0.05$). The relative benefit for achieving an optimal

TABLE 1. Selected baseline characteristics in the 730 PREVER-prevention trial participants

	Intervention ($n = 372$)	Placebo ($n = 358$)
Males	186 (50.0)	179 (50.1)
Age (years)	50 ± 10	50 ± 11
White skin color[a]	195 (52)	206 (58)
Education (years)	11 ± 4	11 ± 4
Body mass index (kg/m^2)	29 ± 5	29 ± 5
SBP (mmHg)	128 ± 7	128 ± 7
DBP (mmHg)	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
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[b] (%)	30 (8)	29 (8)
Current smokers	28 (8)	37 (10)
Current consumption of alcohol	227 (61)	206 (58)

Data displayed as number (%) or mean ± SD.
[a]Self-reported and categorized as white or nonwhite.
[b]Previous physician's diagnosis, use of drugs for diabetes, abnormal fasting glucose or glycosilate hemoglobin at the baseline.

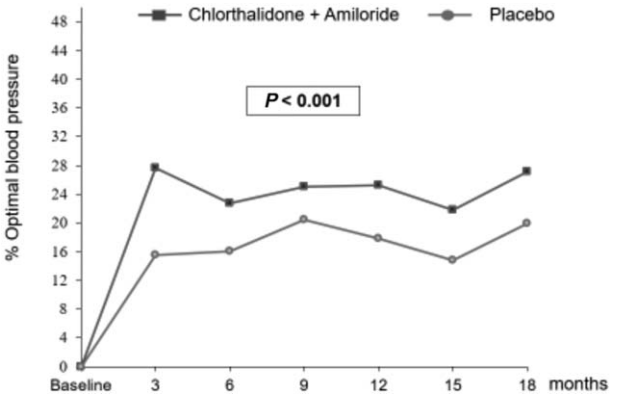

FIGURE 1 Percentage of participants with optimal blood pressure (SBP/DBP <120/80 mmHg) at baseline and during follow-up in those randomized to chlorthalidone and amiloride or placebo.

level of BP at the end of the trial was 1.33 for the chlorthalidone and amiloride group compared with placebo (33% more). The absolute benefit was 6.3% (6.3 more participants who achieved optimal BP per 100 participants treated with diuretics instead of placebo), corresponding to one participant achieving an optimal level of BP for every 16 participants who were treated with low-dose chlorthalidone–amiloride.

Figure 2 shows that at the 18th month visit, there was a leftward shift in the distribution of SBP and DBP in the participants treated with low-dose diuretic. The mean SBP was reduced from 127.9 to 123.3 mmHg in the active intervention group and from 127.3 to 125.5 mmHg in the placebo group, representing a difference in SBP reduction between the two treatment groups of 2.8 (95% CI 1.1 to 4.5) mmHg ($P = 0.001$). The corresponding values for DBP were 80.3–77.9 and 79.8 to 78.5 mmHg, a between-group difference of 1.1 mmHg (95% CI − 0.09 to 2.4; $P = 0.07$). Despite a significant reduction in incidence of hypertension (11.7% in the diuretic arm versus 19.5% in the placebo arm) and an increased percentage of participants with an optimal BP in the diuretic compared with the placebo arm, BP in most participants remained within the prehypertension range or progressed to hypertension during follow-up: 74.5% of participants of the active treatment arm and 80.7% in the placebo arm.

Figure 3 shows the risk ratios for achievement of optimal BP in the two treatment groups, stratified by several conditions of interest. There was no evidence of a significant modification of treatment effect in any of the six subgroups.

DISCUSSION

In this study, treatment with low-dose chlorthalidone with amiloride during 18 months of follow-up resulted in an optimal level of BP in about 33% more participants than in those who received placebo. The corresponding absolute benefit was 6.3%, suggesting that one participant with prehypertension would be expected to achieve an optimal level of BP for every 16 who were treated with low-dose chlorthalidone–amiloride.

The PREVER-prevention trial was primarily designed to investigate the efficacy of low-dose diuretic for prevention of hypertension and target organ damage in adults with prehypertension [28]. The SPRINT results [12], corroborated by several meta-analyses [14–16] suggest that SBP should be reduced to less than 120–130 mmHg in patients with

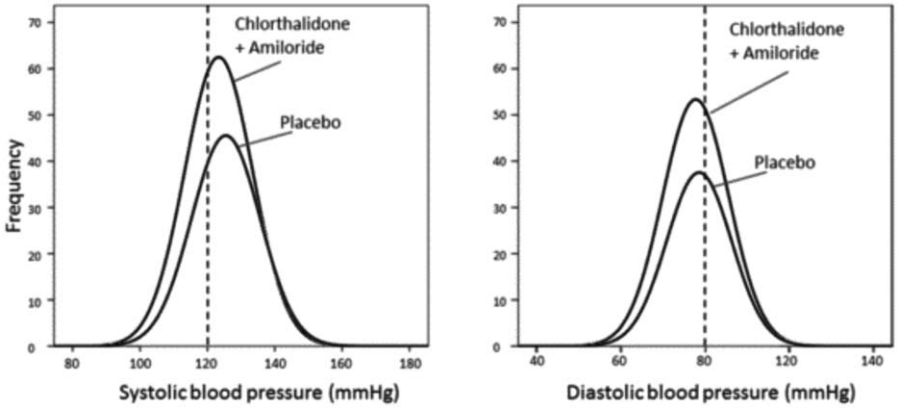

FIGURE 2 Distribution of blood pressure after 18 months of follow-up in patients allocated to the active intervention or placebo.

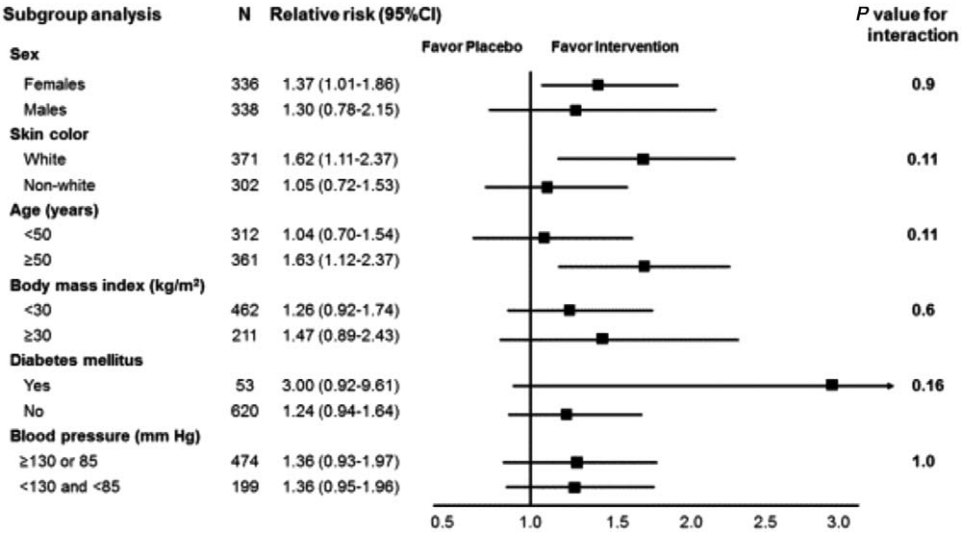

FIGURE 3 Risk ratios for achievement of optimal BP in the two treatment groups, stratified by six subgroups of special interest.

hypertension who are at high risk for CVD. Although direct evidence is lacking, risk estimation and meta-regression of clinical trial experience suggests the corresponding goal for DBP is less than 80 mmHg [30,31]. By analogy, individuals with prehypertension, who do not respond to recommendations for modification of lifestyle, may benefit from drug treatment to reach a SBP/DBP below 120–130/80 mmHg.

The PREVER-prevention trial is one of three intervention studies to demonstrate that low-dose antihypertensive drug therapy is effective in reducing the risk of progressing to hypertension. It is the first to demonstrate benefit for a subclinical marker of CVD (left ventricular mass) and to report the effect of the intervention in normalizing BP. The size of benefit was substantial both for prevention of incident hypertension and achievement of an optimal level of BP. If applied to the general population, the leftward shift of BP demonstrated in the PREVER-prevention trial would be expected to result in an approximately 6% reduction in the risk of coronary heart disease and 15% reduction in the risk of stroke and transient ischemic attack [32]. As far we know, this is the first study to report the effectiveness of drug treatment to reduce blood pressure to optimal values in adults with prehypertension.

Nonetheless, approximately 75% of the participants in the active treatment group continued to have a BP within the prehypertension range. The dilemma of whether or not to initiate antihypertensive drug therapy in adults with prehypertension has to be broadened to a question of whether such therapy should be more intensive in those who fail to achieve an optimal level of BP with low-dose BP-lowering medication. Potentially, the question of whether it is better to employ a lower or higher dosage of antihypertensive drug therapy in adults with prehypertension could be tested in a randomized controlled clinical trial. However, the relatively low absolute incidence of CVD that would be expected in individuals with prehypertension during the usual length of follow up in event-based trials would result in a relatively large sample size. Assuming a 10 mmHg SBP difference in treatment effect, approximately 8000 participants, with a mean SBP of 130 mmHg and an average 10-year CVD risk of at least 5%, would be needed to test the efficacy of a higher versus lower dosage of BP-lowering medication in achieving a 30% reduction in the incidence of major cardiovascular events in 10 years.

In the face of the known risks of prehypertension, and the demonstrated benefits of treatment, a decision to treat prehypertension with low-dose drug therapy in adults who fail to respond adequately to nonpharmacological interventions, and to increase the dose of the antihypertensive drug in those who fail to achieve an optimal level of BP on lower dose therapy, may be justifiable. Further trials designed to investigate the effects of different doses of diuretics, or of combination drug therapy, in individuals who do not achieve an optimal level of BP would be helpful.

A limitation of this report is the post hoc nature of the analysis. However, the fact that the study question complements the original investigation suggests that this is a minor limitation. The relatively large sample size and duration of the trial, the fact that assessment of BP was an integral part of the original design, and the careful planning and conduct of the study are strengths of the PREVER-prevention trial.

In conclusion, use of a fixed combination of low-dose chlorthalidone and amiloride in adults with prehypertension increased the probability of having an optimal level of BP by approximately 33%. However, the large majority of those assigned to active therapy continued to have a BP in the prehypertensive range or progressed to hypertension. Our findings suggest that a higher dose of antihypertensive drug therapy may be desirable in the large number of adults with prehypertension who fail to achieve an optimal level of BP following initiation of nonpharmacological and low-dose active drug therapy.

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Clinical Trial Registration: ClinicalTrials.gov, number: NCT00970931 (https://clinicaltrials.gov/ct2/show/NCT00970931) and REBEC, number: RBR-74rr6s (http://www.ensaiosclinicos.gov.br/rg/RBR-74rr6s/).

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Conflicts of interest

There are no conflicts of interest.

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