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ORIGINAL ARTICLE

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

Flávio D. Fuchs[1] · Luiz C. N. Scala[2] · José F. Vilela-Martin[3] · Paul K. Whelton[4] · Carlos E. Poli-de-Figueiredo[5] · Ricardo Pereira E Silva[6] · Miguel Gus[1] · Luiz A. Bortolotto[7] · Fernanda M. Consolim-Colombo[7] · Rosane P. Schlatter[8] · José E. Cesarino[9] · Iran Castro[10] · José A. Figueiredo Neto[11] · Hilton Chaves[12] · André A. Steffens[13] · João G. Alves[14] · Andréa A. Brandão[15] · Marcos R. de Sousa[16] · Paulo C. Jardim[17] · Leila B. Moreira[8] · Roberto S. Franco[18] · Marco M. Gomes[19] · Abrahão Afiune Neto[20] · Felipe C. Fuchs[1] · Dario C. Sobral Filho[21] · Antônio C. Nóbrega[22] · Fernando Nobre[23] · Otávio Berwanger[24] · Sandra C. Fuchs[1]

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Abstract

Aims To compare the blood pressure (BP)-lowering efficacy of a chlorthalidone/amiloride combination pill with losartan, during initial management of JNC 7 Stage I hypertension in patients with type 2 diabetes mellitus.

Methods In an a priori subgroup analysis of a randomized, double-blind, controlled trial, volunteers aged 30–70 years, with stage I hypertension and diabetes **mellitus**, were randomized to 12.5/2.5 mg of chlorthalidone/amiloride ($N=47$) or 50 mg of losartan ($N=50$), and followed for 18 months in 21 clinical centers. If BP remained uncontrolled after three months, study medication dose was doubled, and if uncontrolled after six months, amlodipine (5 and 10 mg) and propranolol (40 and 80 mg BID) were added as open label drugs in a progressive fashion.

Results Systolic BP decreased to a greater extent in participants allocated to diuretics compared to losartan ($P<0.001$). After 18 months of follow-up, systolic BP was 128.4 ± 10.3 mmHg in the diuretic group versus 133.5 ± 8.0 in the losartan group ($P<0.01$). In the diuretic group, 36 out of 43 participants (83.7%) had a JNC 7 normal BP, compared to 31/47 (66%) in the losartan group ($P=0.089$). Serum cholesterol was higher in the diuretic arm at the end of the trial. Other biochemical parameters and reports of adverse events did not differ by treatment.

Conclusions Treatment of hypertension based on a combination of chlorthalidone and amiloride is more effective for BP lowering compared to losartan in patients with diabetes **mellitus** and hypertension.

Trial registration Clinical trials registration number: NCT00971165

Keywords Hypertension · Diabetes · Drug treatment · Chlorthalidone · Amiloride · Losartan

Introduction

The European Society of Cardiology (ESC)/European Society of Hypertension (ESH) 2018 Guidelines for management of hypertension recommend renin-angiotensin system blockers as preferential agents for the management of hypertension in patients with diabetes mellitus [1]. This preference relies on presumptive pleiotropic effects, particularly of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) [2]. The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guideline [3] advises therapy using agents from any recommended class of first-line antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) in the management of hypertension in patients with diabetes mellitus, with the exception that ACE inhibitors or ARBs may be considered in the presence of albuminuria.

Managed by Massimo Porta.

Hilton Chaves, Abrahão Afiune Neto: in memorial.

✉ Sandra C. Fuchs
sfuchs@hcpa.edu.br

Extended author information available on the last page of the article

The effectiveness of ARB in the prevention of major cardiovascular events and renal disease has been questioned [4]. Some meta-analyses have suggested a lack of efficacy for ARBs in the prevention of myocardial infarction and all-cause mortality [5, 6], including a meta-analysis of trials in patients with type 2 diabetes mellitus [7].

Prior to the PREVER-Treatment trial, the comparative effectiveness of ARBs and diuretics for prevention of cardiovascular and renal disease events had not been assessed in randomized clinical trials. Even the BP-lowering effect of these drugs had not been directly compared in trials with a long period of follow-up before the publication of the PREVER-Treatment trial [8]. In the PREVER-Treatment trial, the combination of chlorthalidone and amiloride was more effective compared to losartan for blood pressure (BP)-lowering in 655 adults not taking BP-lowering medication who had a systolic BP (SBP) 140–159 mm Hg or diastolic BP (DBP) 90–99 mm Hg. In this report, we present the comparative effectiveness of the two treatments in the subgroup of 97 participants with diabetes mellitus who were enrolled in the PREVER-Treatment trial.

Methods

The PREVER-Treatment study was a randomized double-blind controlled trial comparing the BP-lowering effectiveness of chlorthalidone plus amiloride versus losartan for the management of hypertension. The study was registered at clinicaltrials.gov (NCT00971165) trial and the protocol as well as main results have been published [8, 9]. Briefly, the PREVER-Treatment trial was conducted in 21 academic medical centers in Brazil, and was approved by the Research Ethics Board of each participant institution. Starting in July 1, 2010, the enrollment of adults between 30 and 70 years of age with an untreated systolic BP (SBP) 140–159 mm Hg and/or diastolic BP (DBP) 90–99 mm Hg whose BP was not controlled to an SBP < 140 mm Hg and DBP < 90 mm Hg after three months of non-drug recommendations (dietary and physical activity) were eligible to be enrolled in the trial and gave their informed consent prior to their inclusion in the study. Participants were followed for 18 months and the study closed September 30, 2014. This analysis details the results in the 97 PREVER-Treatment participants with type 2 diabetes mellitus. The diagnosis of diabetes was based on a fasting blood glucose ≥ 126 mg.dl or glycated hemoglobin ≥ 6.5% or use of drugs for diabetes at the baseline evaluation.

Participants were centrally randomized at a 1:1 ratio to a chlorthalidone plus amiloride combination pill or to losartan. Randomization was performed by a statistician at the data center using alphanumeric codes and a validated software, with variable block sizes of 4, 6, 8 or 10 and was stratified by center. The randomization list was implemented by the study's website independent of the team that enrolled participants and assigned them to the trial groups. 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 six month visit, amlodipine 5 mg once a day was added, in an open fashion, and increased to 10 mg if necessary at the nine month visit. At the twelve-month visit, propranolol 40 twice a day was prescribed for patients with uncontrolled BP, and the dose was doubled at the fifteenth month visit if necessary. A final visit was conducted after 18 months of follow-up.

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

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

Adverse events were investigated through open questions and use of a semi-structured self-reported questionnaire, which queried presumed adverse effects of the study drugs. Serum potassium, uric acid, glycosylated hemoglobin, fasting serum glucose, serum cholesterol, LDL-cholesterol and triglyceride levels, and microalbuminuria were measured at baseline and the final follow-up visit.

The analysis of patients with diabetes mellitus was specified a priori in the trial protocol, but there was no sample size calculation for this subgroup analysis. 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 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 in the model. The rate of BP control by treatment assignment was compared by means of Chi-square testing at the end of trial. Electrocardiographic estimates of left ventricular mass were compared by use of ANOVA for repeated measurements testing, and biochemical parameters were compared by means of Student's t-test for independent samples. All analyses were performed with SPSS, Version 21.0. Armonk, NY.

Results

In total, 655 participants were enrolled in the main trial. In this a priori analysis, we included the 47 participants in the diuretic group and 50 in the losartan group who had type 2 diabetes mellitus (Fig. 1).

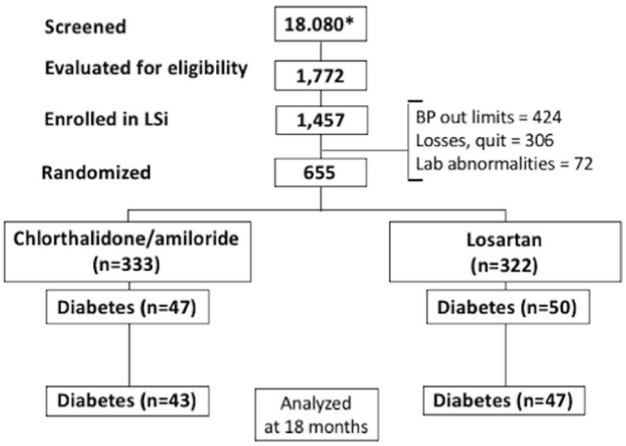

Fig. 1 Flow Diagram showing the progress of the patients throughout the trial

Table 1 shows that there was a similar distribution of baseline characteristics among the treatment arms. The vast majority of trial participants (83%; 43 in the diuretic arm and 47 losartan arm) were evaluated at the final study visit (Fig. 1).

SBP decreased to a greater extent in the participants allocated to diuretics compared to losartan during trial follow-up ($P<0.001$) (Fig. 2). There was also a trend for lower average DBP in the diuretic-based group but this was not statistically significant. After 18 months of follow-up, average SBP was 128.4 ± 10.3 mmHg in participants randomized to diuretic therapy compared to 133.5 ± 8.0 in those randomized to losartan ($P<0.01$). In the diuretic group, 36 out of 43 participants (83.7%) had a SBP/DBP < 140/90 mm Hg at their last study visit, compared to 31/47 (66%) the losartan group ($P=0.09$). The proportion of participants that doubled the dose of the investigational drugs and received additional antihypertensive agents was not substantially different in the two treatment groups (Fig. 2).

Serum cholesterol was higher in the diuretic arm at the end of the trial, with a nominal but unadjusted probability value of 0.042. Other biochemical measurements, including microalbuminuria, did not differ significantly by treatment group (Table 2). In addition, there was no difference in indicators of excess adiposity (BMI, waist circumference and

Table 1 Baseline characteristics of participants with diabetes enrolled in the PREVER-Treatment trial (*N* (%) or mean ± standard deviation)

Characteristics		Chlorthalidone/ Amiloride ($n=47$)	Losartan ($n=50$)	*P* value
Sex	Male	20 (42.6)	27 (57.4)	0.42
Age (years)		55.7 ± 8.7	56.2 ± 7.1	
Skin color	White	24 (51.1)	27 (54.0)	0.84
	Non-white	23 (48.9)	23 (46.0)	0.75
Education (years)		9.0 ± 4.8	10.1 ± 4.1	0.24
Systolic BP (mm Hg)		143.6 ± 6.2	142.4 ± 6.9	0.38
Diastolic BP (mm Hg)		88.4 ± 7.1	88.0 ± 6.7	0.80
Body mass index (Kg/m^2)		31.1 ± 4.9	30.4 (4.7)	0.43
Obese (BMI ≥ 30 kg/m^2)		23 (48.9)	26 (52.0)	0.84
Serum glucose (mg/dl)		153.1 ± 58.2	148.5 ± 65.6	0.71
Glycosylated hemoglobin (%)		7.5 ± 1.8	7.4 ± 2.0	0.79
Total cholesterol (mg/dl)		204.1 ± 36.5	191.3 ± 48.6	0.15
LDL-cholesterol (mg/dl)		119.1 ± 36.9	114.7 ± 33.7	0.08
HDL-cholesterol (mg/dl)		44.9 ± 11.0	46.0 ± 10.8	0.61
Triglycerides (mg/dl)		210.4 ± 130.6	213.4 ± 218.1	0.94
Creatinine (mg/dl)		0.78 ± 0.16	0.84 ± 0.24	0.13
Microalbuminuria		12.9 ± 33.0	14.6 ± 48.8	0.84
Smoking	Current	2 (4.3)	1 (2.0)	0.77
	Never	28 (59.6)	32 (64.0)	
	Past	17 (36.1)	17 (34.0)	
Alcoholic beverage consumption	Current	27 (57.4)	28 (56.0)	0.82
	Never	9 (19.1)	12 (24.0)	
	Past	11 (23.3)	10 (20.0)	

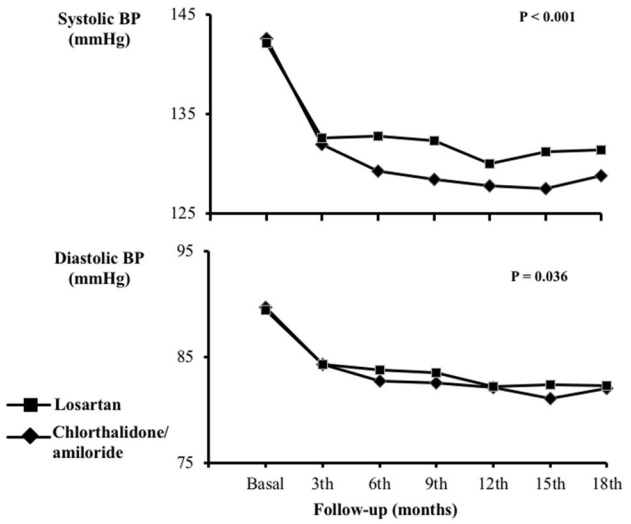

Fig. 2 Systolic and diastolic blood pressure values by study group during follow-up. The number of participants evaluated at each visit and the number who were treated with the higher dosage of their assigned study drug as well as the number that received a prescription for treatment with an open label drug is shown at each visit

Table 2 Laboratory outcomes at 18 months of follow-up (mean ± standard deviation)

	Chlorthalidone/ Amiloride (43)	Losartan (47)	*P*
Serum glucose (mg/dl)	158.7 ± 68.3	145.9 ± 53.9	.33
Glycosylated hemoglobin (%)	7.7 ± 2.0	7.5 ± 2.1	.74
Serum cholesterol (mg/dl)	201.8 ± 42.1	185.2 ± 33.8	.04
LDL-cholesterol (mg/dl)	117.2 ± 35.5	106.3 ± 32.0	.13
HDL-cholesterol (mg/dl)	46.6 ± 12.9	49.0 ± 14.7	.43
Serum potassium (meq/dl)	4.4 ± 0.6	4.5 ± 0.5	.34
Serum creatinine (mg/dl)	0.87 ± 0.22	0.97 ± 0.56	.29
Serum uric acid (mg/dl)	5.6 ± 1.5	5.0 ± 1.4	.09
Microalbuminuria (mg/L)	16.2 ± 26.7	28.5 ± 40.4	.09

waist/hip ratio) by treatment group. Likewise, there was no significant difference in reports or adverse events by treatment group (Table 3).

Discussion

This post-hoc but a priori analysis of the PREVER-Treatment trial showed that the greater BP-lowering effect of chlorthalidone and amiloride compared to losartan, that was observed in the trial as a whole, was also noted in the subset of trial participants with type 2 diabetes mellitus. The magnitude of the BP difference during the trial and at the final visit, after 18 months of treatment, is clinically

Table 3 Self-reported adverse events by treatment arm during trial follow-up*

Number of reports by major groupings	Chlorthalidone/Amiloride (47)	Losartan (50)
Musculoskeletal complaints	12 (25.5)	9 (18.0)
Digestive complaints	5 (10.6)	3 (6.0)
Upper Respiratory Complaints	3 (6.4)	3 (6.0)
Dizziness	3 (6.4)	3 (6.0)
Headache	2 (4.3)	3 (6.0)
Fatigue	2 (4.3)	1 (2.0)
Urinary/Gynecological complaints	2 (4.3)	2 (4.0)
Blood pressure elevation	2 (4.3)	2 (4.0)
Edema	2 (4.3)	1 (2.0)
Sexual complaints	0 (0)	1 (2.0)
Fever	0 (0)	2 (4.0)
Eye disorders	0	2 (4.0)
Dry mouth	2 (4.3)	0 (0)
Others	9 (19.1)	17 (34%)

*Reported at least once by at least one patient

relevant. Based on meta-analysis findings [10], the approximately 5 mm Hg lower level of SBP noted during the last six months of trial follow in the diabetics treated with diuretics SBP would be expected hypothetically to result in approximately 20% fewer strokes and 10% fewer coronary events. The finding that losartan was less effective in lowering BP compared with chlorthalidone may explain, at least in part, meta-analysis reports that angiotensin receptor blockers are less effective for prevention of all-cause mortality and major cardiovascular events [11]. Considering the pivotal role of high BP in the causation of CV disease [12], management of hypertension in patients with diabetes mellitus using diuretics, alone or in combination with other agents, may be optimal, especially in settings where laboratory monitoring is feasible. The association with a potassium-sparing agent would be particularly useful in the treatment with isolated thiazide-like diuretics [13].

Consistent with the overall trial experience and results of larger trials, serum cholesterol levels were higher in the diuretic arm at the end of the trial but the difference was relatively small. The prevention of microalbuminuria with losartan in placebo controlled randomized clinical trials conducted in diabetics with nephropathy, [14, 15] was not identified in our comparison of losartan and a chlorthalidone/amiloride combination pill.

Our findings are limited by the fact that the PREVER-Treatment trial was not designed to compare the effectiveness of diuretics and angiotensin receptor blockers for prevention of major CV events. Another limitation is the post-hoc nature of the analysis and relatively small sample size. Despite this, the sample size was adequate for

detection of a difference in BP and the duration of follow-up (18 months) was longer than in many previous reports of antihypertensive drug treatment in adults with diabetes mellitus. In addition, considerable attention was paid to investigator/staff training and quality control for our BP measurements, the principal outcome of interest. Finally, the participation of more than 20 clinical centers distributed throughout Brazil may be considered another strength of our study.

In conclusion, treatment of hypertension using a combination of chlorthalidone and amiloride was more effective for lowering BP compared with losartan.

Author contributions SCF and FDF have full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors made substantial contributions to the conception of the study, and/or the acquisition, analysis, or interpretation of study data, and/or drafting or revision of the manuscript, and all authors approved the final version of the manuscript and agreed to be accountable for all aspects of the study.

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Availability of data and material (data transparency) All datasets on which the conclusions of the paper rely will be available to in publicly available repository (https://www.lume.ufrgs.br/).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ethics Committee of the Hospital de Clinicas de Porto Alegre (GPPG 08-621), which is accredited by the Office of Human Research Protections as an Institutional Review Board, and by the ethics committee at each medical center. The PREVER-Treatment trial was conducted in 21 academic medical centers in Brazil, and was approved by the Research Ethics Board of each participant institution.

Informed consent Eligible participants were enrolled in the trial and gave written informed consent prior to their inclusion in the study.

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Affiliations

Flávio D. Fuchs[1] · Luiz C. N. Scala[2] · José F. Vilela-Martin[3] · Paul K. Whelton[4] · Carlos E. Poli-de-Figueiredo[5] · Ricardo Pereira E Silva[6] · Miguel Gus[1] · Luiz A. Bortolotto[7] · Fernanda M. Consolim-Colombo[7] · Rosane P. Schlatter[8] · José E. Cesarino[9] · Iran Castro[10] · José A. Figueiredo Neto[11] · Hilton Chaves[12] · André A. Steffens[13] · João G. Alves[14] · Andréa A. Brandão[15] · Marcos R. de Sousa[16] · Paulo C. Jardim[17] · Leila B. Moreira[8] · Roberto S. Franco[18] · Marco M. Gomes[19] · Abrahão Afiune Neto[20] · Felipe C. Fuchs[1] · Dario C. Sobral Filho[21] · Antônio C. Nóbrega[22] · Fernando Nobre[23] · Otávio Berwanger[24] · Sandra C. Fuchs[1]

1 Division of Cardiology, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande Do Sul, INCT PREVER, CPC, 5º. and Ramiro Barcelos, 2350, Porto Alegre, RS 90035-903, Brazil

2 Hospital Universitário Júlio Müller, Universidade Federal de Mato Grosso, Cuiabá, MT, Brazil

3 Faculdade de Medicina São José Do Rio Preto, São José do Rio Preto, SP, Brazil

4 Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, USA

5 Faculdade de Medicina Hospital São Lucas, PUCRS, Porto Alegre, RS, Brazil

6 Hospital Universitário Walter Cantídio, Universidade Federal do Ceará, Fortaleza, CE, Brazil

7 Faculdade de Medicina, Instituto do Coração, Universidade de São Paulo, São Paulo, SP, Brazil

8 Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande Do Sul, Porto Alegre, RS, Brazil

9 Faculdade de Ciências Farmacêuticas, USP Ribeirão Preto, Ribeirão Prêto, SP, Brazil

10 Instituto de Cardiologia, Av. Princesa Isabel, Porto Alegre, RS 395, Brazil

11 Hospital Universitário Universidade Federal do Maranhão, São Luís, MA, Brazil

12 Universidade Federal de Pernambuco, Recife, PE, Brazil

13 Universidade Federal de Pelotas, Pelotas, RS 96010-610, Brazil

14 Instituto de Medicina Integral Prof Fernando Figueira, Recife, PE, Brazil

15 Universidade Do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

16 Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

17 Hospital das Clínicas de Goiânia, Universidade Federal de Goiás, Goiânia, GO, Brazil

18 Faculdade de Medicina de Botucatu, Botucatu, SP, Brazil

19 Hospital do Coração de Alagoas, Maceió, AL, Brazil

20 Anis Rassi Hospital, Goiânia, GO, Brazil

21 Hospital Universitário Procape, Recife, PE, Brazil

22 Hospital Universitário Antônio Pedro, UFF, Niterói, RJ, Brazil

23 Faculdade de Medicina de Ribeirão Preto, USP Ribeirão Preto, Ribeirão Prêto, SP, Brazil

24 Instituto de Pesquisa, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil