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ORIGINAL RESEARCH

Optimizing Blood Pressure Control: A Randomized Comparative Trial of Losartan/Chlorthalidone vs. Losartan/Hydrochlorothiazide

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ABSTRACT

Introduction: Cardiovascular diseases are a leading cause of global mortality, with hypertension as a major risk factor. Low control rates are often attributed to monotherapy, while evidence and clinical guidelines support the effectiveness of combination therapies. This study aimed to evaluate blood pressure changes and the achievement of target levels in patients treated with losartan/chlorthalidone (L/C) compared to losartan/hydrochlorothiazide (L/H).

Methods: A randomized, double-blind, prospective, multicenter clinical trial was conducted. Patients were assigned to one of two treatment groups, starting with a lower dose (50/12.5 mg of losartan/chlorthalidone or losartan/hydrochlorothiazide). Blood pressure was evaluated at 30 days, and patients not meeting therapeutic goals were escalated to a higher dose (100/50 mg of losartan/chlorthalidone or losartan/hydrochlorothiazide) and followed until the study end (60 days).

Results: The study recruited 163 patients (83 for losartan/chlorthalidone [L/C] group and 80 for the losartan/hydrochlorothiazide [L/H] group), with a mean age of 53.1 years. Both treatment groups demonstrated significant reductions in systolic and diastolic blood pressure, with L/C achieving an average reduction in systolic blood pressure (SBP) of – 24.6 mmHg and – 13.3 mmHg for diastolic blood pressure (DBP), while L/H had reductions of – 25.3-mmHg and – 11.5 mmHg, respectively. The L/C group exhibited a higher likelihood of achieving blood pressure goals compared to the L/H. Adverse events were comparable between groups and were mostly mild.

Conclusions: The study showed that both combinations are effective for hypertension, with losartan/chlorthalidone demonstrating

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greater efficacy in reducing diastolic blood pressure and achieving target levels. Both treatments exhibited similar and favorable safety profiles. ***Clinical Trials Registration***: NCT04927299. Registered August 6, 2021-https://clinicaltrials.gov/study/NCT04927299

Keywords: Hypertension; Cardiovascular disease; Losartan; Chlorthalidone; Hydrochlorothiazide

Key Summary Points

In Mexico, nearly 48% of adults are hypertensive, but only 33.7% of diagnosed individuals have controlled blood pressure, highlighting a critical need for effective treatment strategies.

Emerging evidence suggests that chlorthalidone may be more effective than hydrochlorothiazide in managing hypertension, particularly in lowering systolic blood pressure and providing a longer duration of action. Recent guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) recommend chlorthalidone as a preferred diuretic option, emphasizing its efficacy and safety in hypertension treatment.

Both treatment groups exhibited similar safety profiles; however, the fixed-dose combination of losartan/chlorthalidone was shown to be an effective and safe treatment for hypertension, particularly in lowering diastolic blood pressure. This combination therapy may enhance patients' quality of life and reduce the risk of disease progression and complications.

The study demonstrates that both fixed-dose combinations effectively treat hypertension, with losartan/chlorthalidone showing greater efficacy, particularly in diastolic blood pressure (DBP) reduction. This fixed-dose combination increases the likelihood of achieving optimal blood pressure targets.

The safety results indicate a favorable profile for both losartan/chlorthalidone and losartan/hydrochlorothiazide treatments. Adverse events were similar across groups, predominantly mild and expected, suggesting that both treatments are well tolerated and maintain a comparable benefit–risk balance.

INTRODUCTION

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide, with hypertension (HTN) recognized as the most prevalent cardiovascular risk factor. According to the World Health Organization (WHO), approximately 1.28 billion adults aged 30 to 79 are affected by hypertension, with two-thirds residing in low- and middle-income countries [1]. In 2019, the global prevalence of hypertension among adults in the age group of 30 to 79 was estimated at 34% for men and 32% for women [2].

Studies combining population mean blood pressure data with epidemiological risk indices estimate that between 7.7 and 10.4 million deaths annually can be attributed to systemic hypertension. In 2015, around 4.5 million deaths in men and 4 million in women were associated with blood pressure levels exceeding the optimal threshold of 115 mmHg, with 88% of these deaths occurring in low- and middle-income countries [3].

Currently, diverse international guidelines exist for the diagnosis and treatment of hypertension, leading to variations in prevalence estimates depending on the reference used. In Mexico, according to the 2022 National Health Survey (ENSANUT) and based on the criteria published by the American Heart Association (AHA)/American College of Cardiology (ACC), the prevalence of hypertension among Mexican adults aged 20 years and older is estimated to be 47.8%, with only 65.6% being diagnosed and only 33.7% of those previously diagnosed having controlled blood pressure [4].

Hypertension is a multifactorial disease, and its prevalence increases with age. The

Framingham study suggests that 90% of individuals with normal blood pressure at age 55 will develop hypertension at some point in their lives [5]. Aging is associated with microscopic and macroscopic changes in the heart, vascular system, and autonomic nervous system, which can increase inflammation and vascular stiffness, contributing to elevated blood pressure [6].

In this context, early diagnosis and treatment initiation are crucial. Systematic reviews and meta-analyses indicate that a decrease of 10 mmHg in systolic blood pressure (SBP) or 5 mmHg in diastolic blood pressure (DBP) is associated with significant reductions in major cardiovascular events (up to 40% in heart failure, 35% in strokes, 15% in coronary artery disease, 20% in cardiovascular mortality, and 10% in all-cause mortality) [3, 7]. International clinical practice guidelines recommend five main pharmacological classes of medications as first-line antihypertensive agents: thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARA II), calcium channel blockers, and beta-blockers [2, 8]. Diuretics have been essential in hypertension management for decades, with thiazide diuretics recognized as first-line treatments due to their proven efficacy in reducing cardiovascular risk. While hydrochlorothiazide remains the most commonly used, the debate continues between it and chlorthalidone. Combining thiazide diuretics with potassium-sparing agents enhances effectiveness and minimizes adverse effects [9]. One major reason for the low rate of controlled patients is that most of them are being treated with monotherapy, despite evidence that many require combination therapies to achieve optimal blood pressure levels. Fixed-dose combinations (FDC) of two or three antihypertensive medications have shown better outcomes, particularly in patients at risk for cardiovascular events [10, 11].

According to the ACC/AHA guidelines, healthcare professionals are encouraged to "use FDC when available," simplifying pharmacological regimens and benefiting patients through the advantages of these combinations [12]. The WHO 2021 pharmacological treatment guidelines also highlight that drug combinations improve blood pressure control and facilitate the achievement of results more quickly. Combination therapy in a single tablet can enhance adherence to treatment, potentially improving control rates and preventing cardiovascular complications [13].

The rationale for recommending combination therapy, particularly FDC, is based on several considerations: most patients will eventually require two or more antihypertensive agents to achieve blood pressure control; combining agents from different classes increases efficacy in blood pressure reduction; fewer doses of each agent are needed, reducing adverse events; adherence and persistence improve; and polypharmacy is minimized for patients taking additional medications [14].

The FDA has established guidelines for the clinical development of fixed-dose combination (FDC) products for hypertension, noting that most patients require multiple medications for effective blood pressure control. Key considerations include using previously approved antihypertensives with distinct mechanisms, ensuring each component contributes to the claimed effects, and confirming the safety and efficacy of dosages. The trial population must be suitable for therapy initiation, with expected significant effects on both systolic and diastolic blood pressure.

Chlorthalidone and hydrochlorothiazide are both thiazide-type diuretics widely utilized in the management of hypertension. Emerging evidence indicates that chlorthalidone may offer advantages in blood pressure control compared to hydrochlorothiazide, particularly in terms of lowering systolic blood pressure (SBP) and exhibiting a longer duration of action due to its pharmacokinetic characteristics, such as a longer half-life and greater volume of distribution. Recent hypertension guidelines, including those from the American College of Cardiology/American Heart Association ACC/AHA, increasingly advocate for the use of CTD as a preferred option among diuretics in hypertension management, highlighting its potential benefits in terms of efficacy and safety [15, 16]. A phase III randomized, double-blind clinical trial is deemed sufficient to demonstrate

efficacy, incorporating model-based figures for achieving target blood pressure levels [17]. Given the rise in chronic diseases like systemic hypertension and the use of fixed-dose medications, this study aimed to evaluate blood pressure changes and the proportion of patients reaching target levels with losartan/chlorthalidone compared to losartan/hydrochlorothiazide. As secondary objectives, the evaluation of the probability of reaching these targets and safety outcomes were assessed.

METHODS

Design and Patients

A phase IIIb, randomized, double-blind, prospective, multicenter study was conducted to evaluate the efficacy and safety of the fixed-dose combination of losartan/chlorthalidone compared to losartan/hydrochlorothiazide in the treatment of patients with essential hypertension. Participants of any sex aged 18 to 65 years were eligible for the study upon providing written informed consent. Inclusion criteria required essential hypertension, defined as blood pressure levels of ≥ 140/90 mmHg and < 180/110 mmHg. Women of childbearing age were required to use a contraceptive method, be menopausal, or surgically sterile.

Exclusion criteria included medical contraindications to the medications, known hypersensitivity to any components, or other sulfonamides. Individuals with a glomerular filtration rate (GFR) of ≤ 30 ml/min per 1.73 m^2, those currently receiving other diuretics, or with a history of vascular disease or acute renal failure in the past 6 months were also excluded. Additionally, patients with severe complications from type 2 diabetes mellitus, positive pregnancy tests or lactating women, individuals with cancer (except basal cell carcinoma), severe illnesses deemed serious by the investigator, mental health disorders, gout, or potential conflicts of interest related to the research center or sponsor were not eligible for participation (Fig. 1).

Eligible patients were randomly assigned to one of two groups: group A received losartan 50 mg/chlorthalidone 12.5 mg, with potential escalation to losartan 100 mg/chlorthalidone 25 mg, while group B received losartan 50 mg/hydrochlorothiazide 12.5 mg, escalating to losartan 100 mg/hydrochlorothiazide 25 mg if therapeutic targets were not achieved.

Patients not achieving therapeutic targets—defined as a reduction in systolic/diastolic blood pressure of 20/10 mmHg or reaching blood pressure < 140/90 mmHg—were escalated to the next dose after 30 days. The treatment was administered orally (PO), one tablet per day for 2 months. An evaluation was conducted at 30 days of follow-up or during an unscheduled visit to determine if dose escalation was needed. The study was double-blind, blinding was ensured through uniform packaging and labeling, in addition to the designation of a specific individual for medication distribution. Patients' randomization was conducted using a simple random assignment procedure through the program http://www.randomizer.org, and balanced by treatment. Blood pressure was measured using a validated device (Omron HBP1300) after a 5-min rest, with three consecutive measurements taken to determine the average. Participants maintained a diary to record symptoms and medication intake, which was reviewed during visits to verify adherence and monitor for any signs or symptoms that may have occur during their participation. Finally, laboratory tests were conducted during baseline and final visits, which include blood chemistry panel and a complete blood count.

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines. The Institutional Ethics Committee (IRB) and the Research Committee of Investigación Biomédica para el Desarrollo de Fármacos S.A. de C.V. approved the study (Protocol approval number: CEI-000002), including all the documents used throughout the execution of the study. Additionally, approval was obtained from the Ministry of Health in Mexico, Federal Commission for the Protection against Sanitary Risks (COFEPRIS, Approval No. 223300410A0096/2021) for the execution of the study. All patients provided written informed consent, prior to their inclusion to the clinical

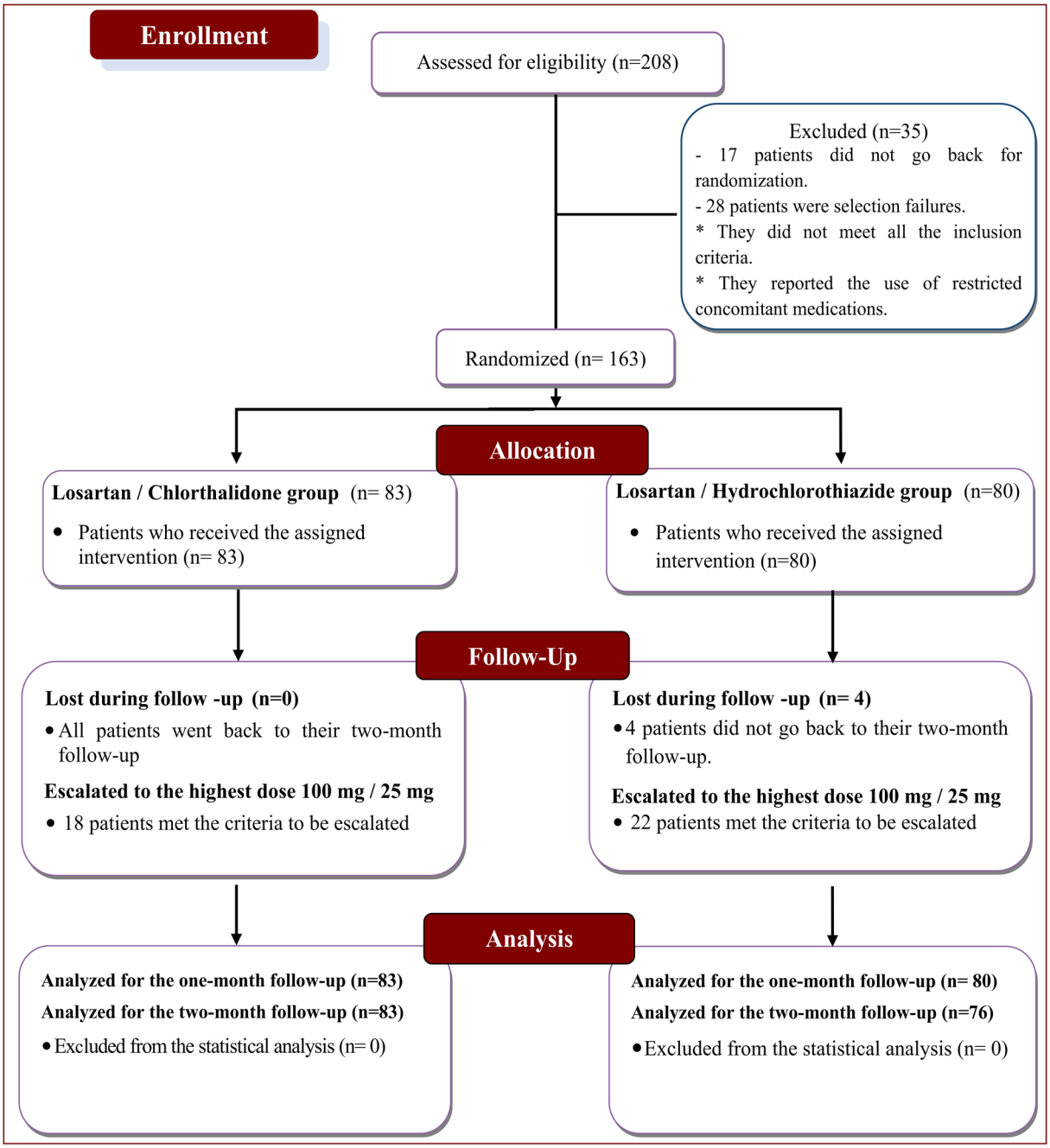


Fig. 1 Flowchart of study patients' enrollment and allocation

trial, where the procedures to be carried out during the follow-ups were explained to them in detail. The study protocol was registered at clinicaltrials.gov (Number: NCT04927299) on August 6, 2021.

Outcome Measures

The primary efficacy outcomes were defined in terms of therapeutic goals, specifically a reduction of 20 mmHg in systolic blood

pressure (SBP) and 10 mmHg in diastolic blood pressure (DBP) from baseline values, or achieving blood pressure levels below 140/90 mmHg, calculated by comparing the average reductions of each parameter to baseline values, in accordance with the International Society of Hypertension Global Practice Guidelines [18]. As secondary endpoints, in line with FDA recommendations detailed in the "Hypertension: Developing Fixed-Combination Drug Products for Treatment" guideline, [17] the probability of achieving these target levels was assessed based on the initial blood pressure of each patient. Considering the previously mentioned, the proportion of patients in each treatment group who achieved their therapeutic goals at 1 and 2 months, as well as the changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) values and their average changes throughout the study were evaluated. The outcome measure assesses the efficacy of treatment in reaching specific target blood pressure levels for SBP and DBP, using increments of 5 mmHg, as reductions of this magnitude are deemed clinically significant according to guidelines.

For safety outcomes, documented adverse events were summarized by treatment group and categorized based on frequency, severity, and causality using the Medical Dictionary for Regulatory Activities (MedDRA).

Statistical Analysis

The hypothesis of the present study stated that the proportion of subjects achieving therapeutic goals (defined as a reduction in systolic/diastolic blood pressure of 20/10 mmHg or reaching blood pressure < 140/90 mmHg) after 2 months of treatment would be 15% higher in the L/C group than in the L/H treatment group. Sample size was calculated for comparison of two independent proportion, considering a probability of at least 70% of response in blood pressure control in the group receiving L/C, compared to 55% in the L/H group, a total difference of 15% between groups, with a statistical power of 80%, an alpha (α) value of 0.05 and a 10% loss rate, obtaining a total of 87 patients per group [19]. An exploratory analysis was conducted to assess the nature and distribution of the variables with the aim of identifying outliers, atypical values, or missing data. For the quantitative variables, Kolmogorov–Smirnov tests were performed to determine if they fit the assumptions of normality, presenting numerical variables with measures of central tendency and dispersion, and categorical variables as frequencies and percentages. The average change in blood pressure (BP) values at 1 and 2 months compared to baseline measurements was evaluated by treatment group (using the final dose) through a repeated measures analysis of variance (ANOVA) with post hoc comparisons adjusted by Bonferroni. Additionally, the magnitude of change for both months was assessed, using the paired samples *t* test or Wilcoxon signed-rank test depending on the data distribution. For comparisons between groups, the Mann–Whitney *U* test was employed. The proportion of subjects who achieved a reduction in systolic/diastolic blood pressure (SBP/DBP) of 20/10 mmHg from their baseline values or BP < 140/90 mmHg was evaluated using the Chi-square test. Forest plots were created to show the probability of achieving therapeutic targets, as well as the mean differences in patients who achieved these targets. Similarly, graphs were created showing the proportion of patients achieving reductions at different blood pressure cutoffs: 10, 15, 20, and 25 mmHg for SBP and 5, 10, 15, and 20 mmHg for DBP. Finally, in accordance with the FDA guidance document "Developing Fixed-Combination Drug Products for Treatment Guidance for Industry," [17] graphs were generated showing the probability of achieving therapeutic targets of SBP < 140 mmHg and DBP < 90 mmHg, considering each patient's baseline value. An analysis was conducted including gender and body mass index (BMI) as covariates. Adverse events were summarized by frequency counts and percentages, categorized by organ/system, and compared between treatment groups using forest plots. A p value < 0.05 indicated statistical significance. All analyses were conducted using IBM SPSS software, v.29.0 for Windows.

RESULTS

Baseline Characteristics

A total of 163 patients with essential systemic hypertension were included. The mean age was 53.1 ± 8.5 years, with 54.6% female. The median body mass index (BMI) was 30.6 kg/m^2, and median waist circumference was 102.2 cm, indicating a high prevalence of overweight or obesity. Baseline measurements showed no significant differences between treatment groups, confirming comparability. The most common comorbidity was type 2 diabetes mellitus (52.6%), followed by dyslipidemia (36.8%) and hypothyroidism (8.4%). Additionally, 56.4% used concomitant medications, with 31.5% consuming alcohol and 18.5% using tobacco (Table 1).

Efficacy Results

Table 2 presents changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) over the follow-up period by treatment group. In the losartan/chlorthalidone (L/C) group, there was a significant decrease in both SBP and DBP at 2 months ($p = 0.001$). The SBP decreased from baseline to 125.0 mmHg, while DBP dropped to 80.6 mmHg. The losartan/hydrochlorothiazide (L/H) group also showed significant reductions in SBP and DBP ($p = 0.001$), with SBP decreasing to 126.8 mmHg and DBP to 82.3 mmHg. However, no significant differences were found between the groups at 1 or 2 months.

The average chance in both blood pressure parameters was evaluated between groups (Table 3). Both the L/C and L/H groups demonstrated significant reductions in SBP and DBP at 1 and 2 months. However, there were no significant differences between groups for either systolic or diastolic blood pressure. The analysis by dose revealed a reduction in both SBP and DBP across both treatment groups. In the L/C group, the lower dose (50/12.5 mg) achieved an average SBP reduction of – 26.6 mmHg, while the higher dose (100/25 mg) resulted in – 21.3 mmHg, with significant differences ($p = 0.029$). For the L/H group, the lower dose reduced SBP by – 28.0 mmHg, compared to – 16.6 mmHg for the higher dose, also significant ($p < 0.001$). In terms of DBP, the L/C group showed reductions of – 16.0 mmHg at 50/12.5 mg and – 8.3 mmHg at 100/25 mg ($p < 0.001$). The L/H group had DBP reductions of – 12.6 mmHg for the lower dose and – 5.6 mmHg for the higher dose, both significant ($p < 0.001$). Comparisons between groups at both doses did not show significant differences.

The L/C treatment group demonstrated greater efficacy than the L/H group in achieving significant reductions in blood pressure after one and two months (Fig. 2). After one month, a higher percentage of patients treated with L/C achieved at least a 10-mmHg reduction in systolic blood pressure (SBP), with improvements noted by the two-month mark. For diastolic blood pressure (DBP), patients treated with L/C also showed favorable results, with a notable increase in those achieving a ≥ 5 mmHg reduction over time. These findings indicate that L/C is more effective in meeting higher therapeutic targets for blood pressure control.

These results indicate that L/C is more effective in achieving higher therapeutic targets for blood pressure control. Considering the specific targets established by guidelines, the results showed that in the L/C group, 68.7% achieved a ≥ 20 mmHg reduction in SBP, with a trend favoring women ($p = 0.053$). In the L/H group, 63.7% met the same target ($p = 0.072$). For a ≥ 10 mmHg reduction in DBP, 69.9% in L/C and 61.3% in L/H achieved this goal, with no significant differences. Regarding the target of < 140/90 mmHg, 85.5% in L/C and 75.0% in L/H met the target, with a significant difference favoring L/C among women ($p = 0.044$).

The study also assessed the mean differences in SBP and DBP among patients achieving these therapeutic targets in both treatments (Fig. 3a). Patients reaching the target of < 140/90 mmHg showed greater reductions in both systolic and diastolic blood pressure with L/C compared to L/H. Specifically, L/C achieved a SBP reduction of – 26.6 mmHg compared to – 21.3 mmHg for L/H, and a DBP reduction of – 16.3 mmHg versus – 14.3 mmHg for L/H. The overall mean difference favored L/C by – 2.03 mmHg,

Table 1 Baseline comparison of demographic, anthropometric, biochemical, and clinical characteristics by treatment group

Characteristics	Total ($n = 163$)	Losartan/chlortalidone $n = 83$ (%)	Losartan/hydrochlorothiazide $n = 80$ (%)	p
Age, years (mean, SD)	53.1 ± 8.5	53.3 ± 8.8	52.9 ± 8.2	0.822
Gender (*n*, %)				
Male (*n*, %)	74 (45.4)	35 (42.2)	39 (48.8)	0.399
Female (*n*, %)	89 (54.6)	48 (57.8)	41 (51.2)	
Weight, kg (median, IQR)	82.5 (71.5, 94.9)	81.9 (70.9, 95.0)	84.9 (72.1, 93.8)	0.771
BMI, kg/m^2 (median, IQR)	30.6 (27.8, 33.7)	30.2 (27.4, 33.4)	31.3 (28.2, 33.7)	0.341
Heart rate, bpm (mean, SD)	76.0 ± 10.4	75.8 ± 10.6	76.7 ± 10.3	0.730
SBP mmHg (median, IQR)	149.0 (143.0, 155.0)	150.3 (143.3, 156.0)	147.5 (143.0, 153.8)	0.321
DBP mmHg (median, IQR)	93.6 (91.6, 96.3)	94.0 (92.0, 96.3)	93.5 (91.6, 96.0)	0.372
Glucose (mg/dl)	94.0 (86.0, 109.0)	96.0 (88.0, 111.0)	92.0 (85.2, 106.2)	0.208
Ureic nitrogen (mg/dl)	13.9 (11.7, 16.6)	13.9 (11.8, 16.0)	13.9 (11.4; 17.3)	0.977
Urea (mg/dl)	30.0 (25.0; 36.0)	30.0 (25.0; 34.0)	30.0 (24.2; 37.0)	0.993
Creatinine (mg/dl)	0.73 (0.64; 0.87)	0.72 (0.64; 0.87)	0.74 (0.65; 0.89)	0.466
Sodium (mmol/l)	138.8 ± 2.3	138.5 ± 2.3	139.0 ± 2.3	0.089
Potassium (mmol/l)	4.1 ± 0.3	4.1 ± 0.3	4.0 ± 0.3	0.191
Chloride (mmol/l)	104.1 ± 2.5	103.8 ± 2.6	104.4 ± 2.4	0.184
Calcium (mg/dl)	9.3 ± 0.3	9.3 ± 0.3	9.2 ± 0.3	0.520
Total, cholesterol (mg/dl)	182.0 ± 37.8	182.2 ± 38.9	179.0 ± 36.6	0.832
HDL cholesterol (mg/dl)	43.9 (36.6; 50.1)	42.0 (36.8; 48.8)	44.6 (36.3; 52.0)	0.442
LDL cholesterol (mg/dl)	109.4 ± 36.4	108.3 ± 34.9	108.1 ± 38.4	0.858
VLDL cholesterol (mg/dl)	28.9 ± 13.6	28.0 ± 8.9	29.5 ± 17.5	0.412
Triglycerides (mg/dl)	151.0 (115.0; 205.5)	152.0 (115.0; 218.0)	149.0 (115.0; 199.0)	0.787
Aspartate aminotransferase (U/l)	20.0 (16.0; 26.0)	20.0 (16.0; 26.0)	20.0 (16.2; 26.0)	0.705
Alanine aminotransferase (U/l)	22.0 (18.0; 30.0)	22.0 (18.0; 30.0)	23.0 (17.0; 30.0)	0.642
Years since diagnosis (median, IQR)	6.0 (3.0; 14.0)	7.0 (3.0; 16.0)	6.0 (3.0; 13.5)	0.499
Glomerular filtration rate (median, IQR)	96.7 (84.5; 104.4)	97.3 (88.3; 103.6)	96.1 (81.2; 104.5)	0.606
Comorbidities (*n*, %)	95 (58.2)	48 (57.8)	47 (58.7)	1.000
Diabetes	50 (52.6)	29 (60.4)	21 (44.6)	0.183
Dyslipidemia	35 (36.8)	15 (31.2)	20 (42.5)	0.352
Hypothyroidism/goiter	8 (8.4)	4 (8.3)	4 (8.5)	1.000
Concomitant medications (*n*, %)	92 (56.4)	48 (57.8)	44 (55.0)	0.716

SBP systolic blood pressure, *DBP* diastolic blood pressure, *mmHg* millimeters of mercury, *mg/dl* milligrams/deciliter. Means and standard deviations (SD) for normal distribution variables compared with independent t test between groups (p). For non-normal distribution variables, medians and interquartile range (IQR) and Mann–Whitney U test. Chi-square for categorical variables

Table 2 Change in systolic and diastolic blood pressure at 1 and 2 months compared to baseline by treatments

Variable Median, IQR	Losartan/chlortalidone ($n=83$)			p^*	Losartan/hydrochlorothiazide ($n=80$)			p^*	p^+	$p^\wedge$
	Baseline	Month 1	Month 2		Baseline	Month 1	Month 2			
Systolic blood pressure (mmHg)	150.3 (143.5; 156.0)	128.0 (121.8; 137.8)	125.0 (118.5; 134.5)	0.001	148.3 (143.1; 154.1)	128.1 (120.8; 138.1)	126.8 (117.0; 135.5)	0.001	0.770	0.702
Diastolic blood pressure (mmHg)	94.0 (92.0; 96.3)	83.0 (76.1; 89.6)	80.6 (74.0; 85.3)	0.001	93.6 (91.6; 96.1)	84.1 (78.6; 88.1)	82.3 (77.6; 87.1)	0.001	0.213	0.080

P^* = Comparison between the three visits, using Friedman's test for related samples, adjusted by Bonferroni. Differences are observed between visits at 1 month vs. baseline and 2 months vs. baseline, not between 1 vs. 2 months. P^+ = Comparison between groups at 1 month. $P^\wedge$ = Comparison between treatments at 2 months. Comparisons were made using the Mann–Whitney U test

highlighting its enhanced efficacy in hypertension management.

To corroborate the results regarding therapeutic targets, an analysis of the overall risk of failing to meet these goals, based on International Society of Hypertension guidelines, was conducted and presented in a forest plot (Fig. 3b). Although the 95% confidence intervals for the measured variables crossed one, indicating non-significant differences between treatments, the overall effect test showed a significant difference in performance between treatments. Specifically, treatment with losartan/chlorthalidone was associated with a better likelihood of achieving therapeutic goals compared to losartan/hydrochlorothiazide.

In accordance with the FDA guideline "Hypertension: Developing Fixed-Combination Drug Products for Treatment Guidance for Industry" the probability of achieving target blood pressure levels (systolic < 140 mmHg and diastolic < 90 mmHg) was calculated, using the means and standard deviations from each patient included in the study. Predictive models were employed to create probability curves based on baseline blood pressure data, allowing the assessment of the likelihood of reaching these targets, which categorized patients as either successful or unsuccessful in achieving therapeutic goals.

As illustrated in Fig. 4a, the probability curve for the losartan/chlorthalidone treatment consistently remains above that of losartan/hydrochlorothiazide across all baseline SBP levels, indicating a significantly higher probability of achieving the < 140 mmHg target ($p=0.001$). Similarly, Fig. 4b shows the probability curve for losartan/chlorthalidone also exceeds that of losartan/hydrochlorothiazide for all baseline DBP levels, suggesting a greater likelihood of reaching the < 90 mmHg target, also statistically significant ($p=0.001$). Finally, an analysis was conducted including gender and body mass index (BMI) as covariates, and no effect of these on the primary variables was observed.

Table 3 Average change in systolic and diastolic blood pressure at 1 and 2 months of treatment

Variable	Losartan/chlortalidone ($n = 83$)		p^*	Losartan/hydrochlorothiazide ($n = 80$)		p^*	p^+	$p^\wedge$
	Month 1	Month 2		Month 1	Month 2			
Systolic blood pressure (mmHg)	– 21.0 (– 12.6; – 30.0)	– 24.6 (– 18.0; – 35.0)	0.009	– 19.5 (– 9.5; – 29.3)	– 25.3 (– 15.5; – 30.6)	0.005	0.443	0.488
Diastolic blood pressure (mmHg)	– 12.3 (– 4.3; – 19.0)	– 13.3 (– 8.6; – 21.3)	0.003	– 11.0 (– 4.3; – 15.2)	– 11.5 (– 6.3; – 17.1)	0.045	0.143	0.068

P^* = Comparison of 1 vs. 2 months within the same treatment, P^+ = Comparison of 1 month between treatments, $P^\wedge$ = Comparison of 2 months between treatments. For comparisons within the same group Wilcoxon signed-rank test for non-normally distributed variables was used. Mann–Whitney *U* test for comparison between groups

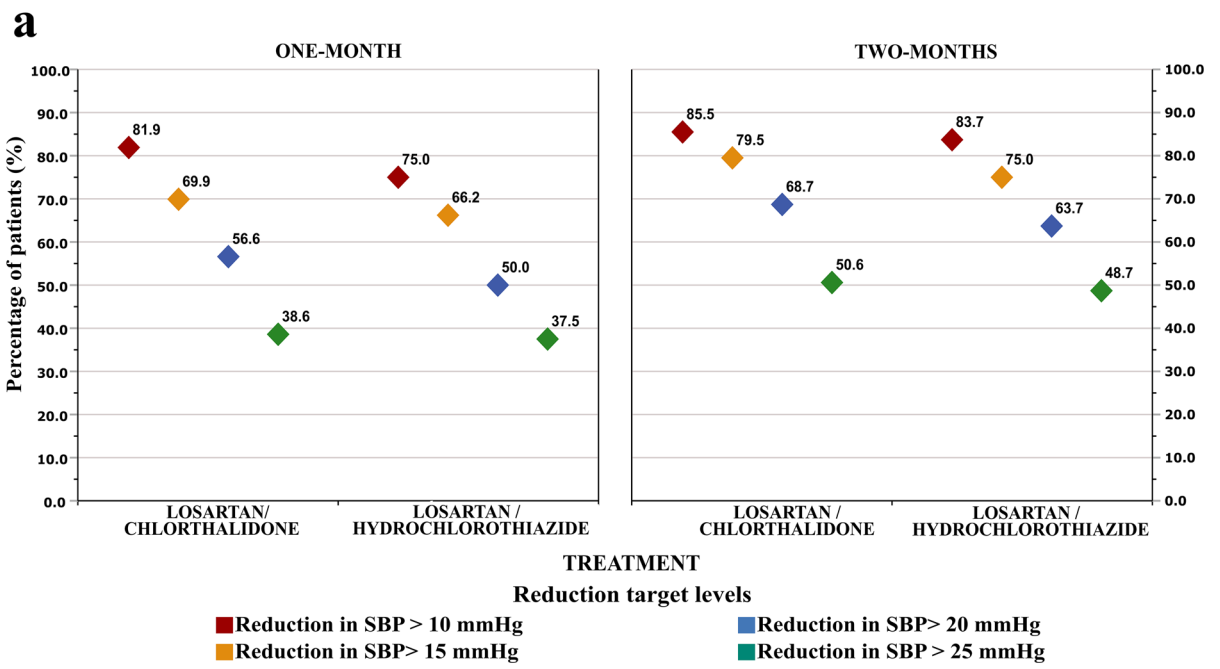
Safety Results

For the safety analysis, all subjects who received at least one dose of any of the investigational products (losartan/chlorthalidone or losartan/hydrochlorothiazide) were evaluated. The results demonstrated a favorable safety profile for both treatments. A total of 63 subjects experienced at least one adverse event (AE), with 32 in the losartan/chlorthalidone group reporting 66 AEs, and 31 in the losartan/hydrochlorothiazide group reporting 54 AEs. The mean age of those with AEs was 51.9 ± 6.8 years, and 60.3% of the affected population were women. In the L/C group, women constituted 56.2%, while in the L/H group, they made up 64.5%. Comparisons of patient characteristics by treatment group showed no clinically or statistically significant differences (Table 4). The analysis of the documented adverse events was conducted according to their severity, intensity, relatedness, and expectedness. The information is presented by the treatment group and the dose at which the event occurred, in Table 5. All the AEs were resolved without complications and no serious adverse events occurred in either treatment group during the study execution.

Furthermore, it was observed that AE in the system, organ, and class (SOC) category of "central nervous system disorders" were the most frequent, occurring in 50.0% of the L/C group compared to 48.1% in the L/H group. In both groups, the most common adverse event was headaches, with 34.8% reports L/C group versus 31.5% in the L/H group. Adverse events classified as definitely related were plotted using a forest plot, with headache being the most common in the L/C group and dizziness in the L/H group. Figure 5 shows the risk differences with their corresponding 95% confidence intervals for each event. The overall effect tests indicate that there are no significant differences in the frequency of adverse events between the two treatments overall.

DISCUSSION

This comparative study of losartan/chlorthalidone (L/C) versus losartan/hydrochlorothiazide (L/H) demonstrates significant reductions in both systolic and diastolic blood pressure, showing that L/C is preferable to standard treatment in achieving therapeutic targets (systolic < 140 mmHg and diastolic < 90 mmHg). This finding may imply a reduction in the risk of both short- and long-term cardiovascular



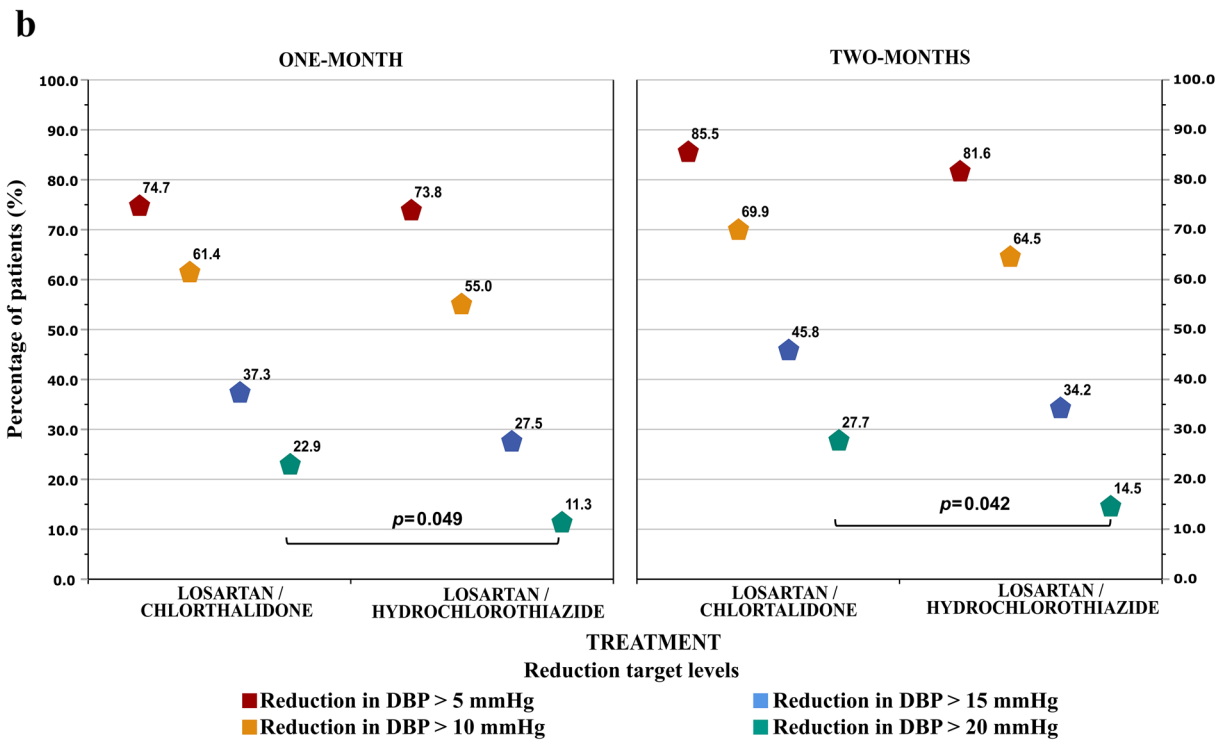


Fig. 2 Proportion of patients at different target values for systolic and diastolic blood pressure by treatments. **a** SBP, distolic blood pressure comparison. **b** DBP, diastolic blood pressure. *The comparison between follow-ups within the same group was conducted using McNemar test. For comparison between groups Chi-square test was used

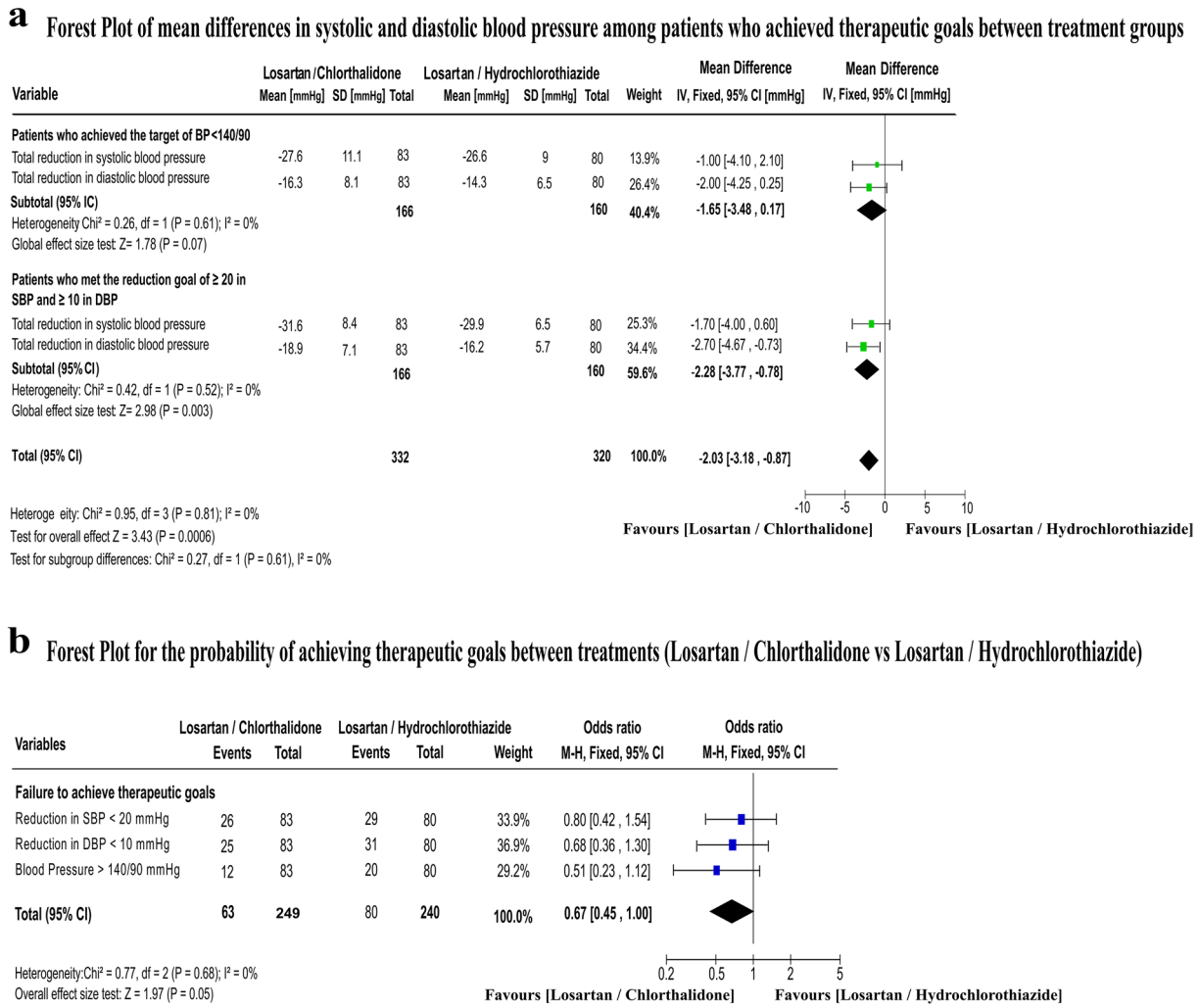


Fig. 3 Forest plots of mean differences in systolic and diastolic blood pressure among patients meeting therapeutic goals and probability of treatment failure. **a** Mean difference in blood pressure. **b** Probability of achieving therapeutic goals

complications. Regarding safety, no statistically significant differences in adverse events were found between treatment groups, confirming that the safety profile of both fixed-dose combinations is favorable.

According to FDA guidance on fixed-dose combinations for hypertension, the study followed recommendations for developing such products. Two antihypertensives, losartan and chlorthalidone, both approved in Mexico for over 20 years, were selected. Their distinct mechanisms allow for additive effects in treatment, with non-maximal doses that help reduce adverse events [17, 20].

The results align with existing literature supporting the efficacy of both agents in lowering blood pressure. Observational studies and reviews have concluded that while both chlorthalidone and hydrochlorothiazide are effective, there is clinical evidence suggesting that chlorthalidone may be 1.5 to 3 times more potent. This study reinforces the notion that patients treated with L/C are more likely to reach therapeutic goals, highlighting a

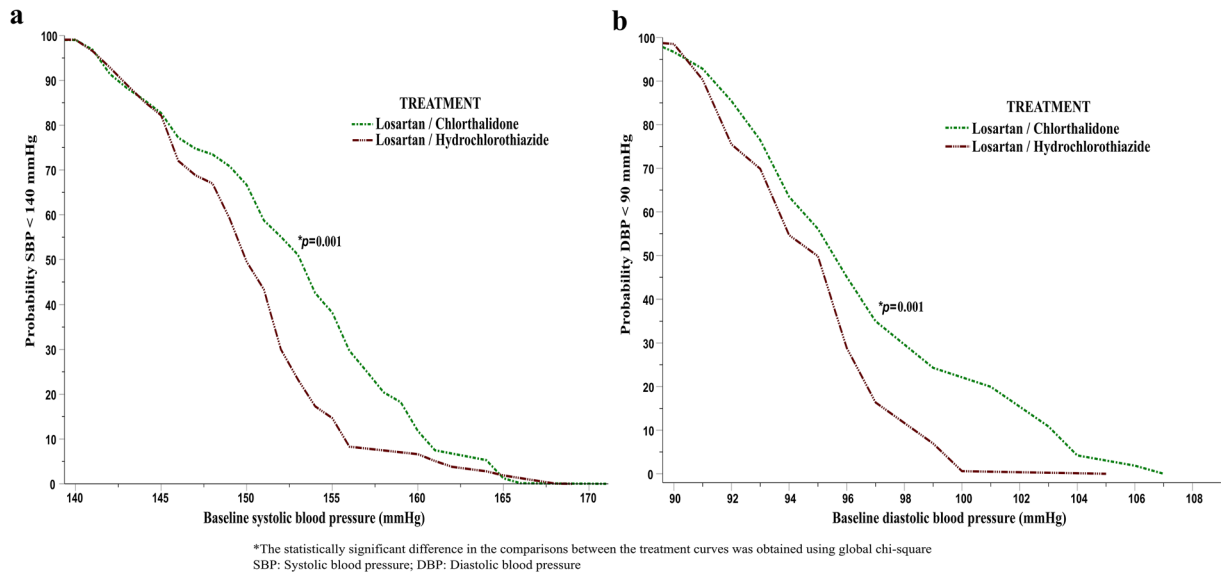


Fig. 4 Forest plot of probability of achieving systolic and diastolic blood pressure target levels by treatments. **a** Probability curve for sistolic blood pressure. **b** probability curve for diastolic blood pressure

significant advantage in hypertension management [21–23].

According to the 2017 ACC/AHA guidelines, thiazides and thiazide-like diuretics are recommended as first-line treatments. Although hydrochlorothiazide is the most commonly prescribed drug in this category, the guidelines indicate that chlorthalidone is preferred due to its longer half-life and proven ability to reduce cardiovascular diseases in clinical trials. The observed effect on vascular permeability may contribute to a reduced risk of cardiac diseases, which is particularly relevant given that hypertension is the most prevalent cardiovascular risk factor, associated with increased risks of heart failure, stroke, coronary artery disease, and cardiovascular mortality [12, 17, 24, 25].

Table 4 Characteristics of patients presenting adverse events during the study by treatment group

Variables for patients	Total $n = 163$ (%)	Treatments		*p*
		Losartan/ chlortalidone ($n = 83$)	Losartan/ hydrochlorothiazide ($n = 80$)	
Number subjects	63 (38.6%)	32 (38.5)	31 (48.3)	1.000
Age, years (mean, SD)	51.9 ± 6.8	53.4 ± 7.6	50.1 ± 5.3	0.009
BMI, kg/m^2 (mean, SD)	31.3 ± 5.2	31.5 ± 6.0	31.1 ± 4.1	0.633
Gender (*n*, %)				
Male	25 (39.7)	14 (43.8)	11 (35.5)	0.609
Female	38 (60.3)	18 (56.2)	20 (64.5)	

Variables are described with means and standard deviations (SD) and compared between groups using Student's *t* tests for independent samples. Categorical variables were described using frequencies and percentages and compared using Chi-square tests

Table 5 Classification of the adverse events presented during the study by treatment group and dosage

Adverse events classifications	Losartan/chlortalidone			Losartan/hydrochlorothiazide			*p*
	Total *n* = 66 (%)	50/12.5 mg *n* = 58	100/25 mg *n* = 8	Total *n* = 54	50/12.5 mg *n* = 52	100/25 mg *n* = 2	
Severity (n, %)							
Mild	43 (65.1)	37 (63.8)	6 (75.0)	39 (72.2)	37 (71.2)	2 (100.0)	0.607
Moderate	23 (34.8)	21 (36.2)	2 (25.0)	15 (27.7)	15 (28.8)	0 (0.0)	
Relatedness (n, %)							
Definitely related	9 (13.6)	6 (10.3)	3 (37.5)	8 (14.8)	7 (13.5)	1 (50.0)	1.000
Possibly related	55 (83.4)	50 (86.2)	5 (62.5)	45 (83.3)	44 (84.6)	1 (50.0)	1.000
Not Related	2 (3.0)	2 (3.5)	0 (0.0)	1 (1.9)	1 (1.9)	0 (0)	1.000
Expectedness (n, %)							
Unexpected	49 (75.4)	42 (72.4)	7 (87.5)	40 (72.5)	38 (73.1)	2 (100.0)	0.668
Expected	17 (24.6)	16 (27.6)	1 (12.5)	14 (27.5)	14 (26.9)	0 (0.0)	

Data is described as frequencies and percentages. Chi-square tests were used for comparisons between treatment groups, not between doses

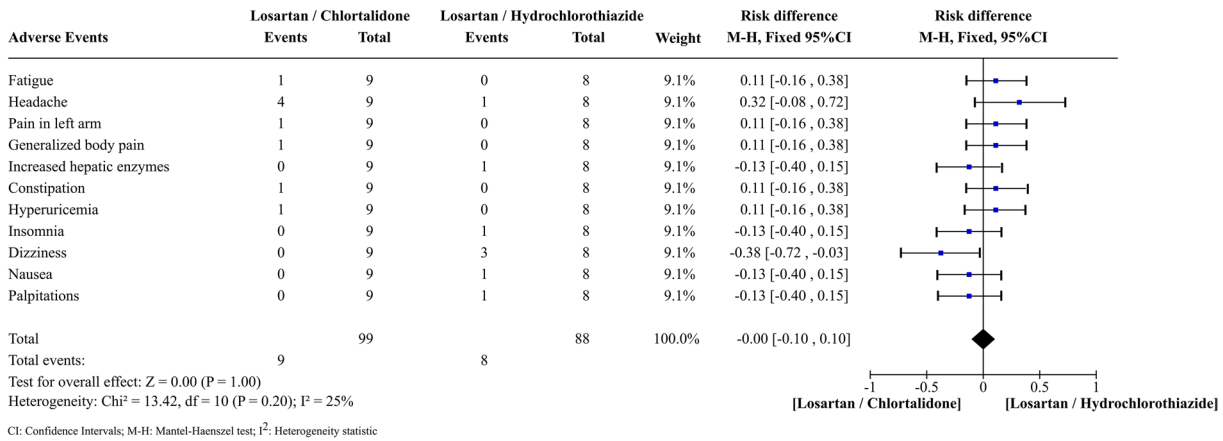


Fig. 5 Forest plot of risk differences for definitely related adverse event frequencies across treatments

Finally, clinical evidence indicates that patients treated with monotherapy often fail to achieve therapeutic goals. This is the reason why the preference for these combinations over separate medications lies in their ability to simplify treatment regimens, facilitating blood pressure control in a shorter time. Additionally, the use of fixed-dose combinations improves adherence and persistence to medication, as fewer doses of each agent are required, which in turn reduces the incidence of adverse events and decreases polypharmacy

in patients who often take multiple medications. This approach has been backed by various international clinical guidelines, including the ACC/AHA (2017), the European Society of Hypertension (ESH, 2023), and the WHO (2021), which recommend initiating treatment with two or more antihypertensives from different classes, rather than opting for monotherapy [11, 12].

Study Limitations

This study has several limitations. The follow-up duration of only two months might not adequately capture the long-term efficacy and safety of the treatments. Additionally, the study did not assess long-term cardiovascular outcomes. It is crucial to note that potential confounding factors, such as variations in participants' lifestyle habits (including diet and physical activity) were not systematically controlled or measured. This limitation primarily arises from the two-month follow-up duration, which restricted the capacity to evaluate the long-term effects of these lifestyle changes. Finally, the high prevalence of specific comorbidities in the study population may not reflect the overall population of patients with hypertension.

CONCLUSIONS

The fixed-dose combination of losartan and chlorthalidone has been shown to be an effective and safe therapeutic option for treating adults with hypertension, particularly in reducing diastolic blood pressure.. The literature emphasizes the advantages of chlorthalidone and the benefits of using fixed-dose combinations compared to administering drugs separately. This suggests that the combination L/C may be a valuable therapeutic alternative, potentially improving patient quality of life and significantly reducing the risk of disease progression and complications both in the short and long term. Future research should include a comprehensive assessment of these lifestyle factors and a more diverse patient population to ensure the generalizability of findings alongside the possibility of doing studies with an extended time that helps to understand long-term effects and safety issues, and to better isolate the effects of the treatments being studied.

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Data Availability. Data will be available upon request to the corresponding author, e-mail: jogonzalez@silanes.com.mx.

Declarations

Conflict of Interest. Isabel E. Rucker-Joerg, Ernesto G. Cardona-Muñoz, Francisco G. Padilla-Padilla, and Rodrigo Suarez-Otero confirm that they have no conflicts of interest to declare. Jorge Alejandro Gonzalez Canudas, Emmanuel Canales-Vázquez, Yulia Romero-Antonio, Kevin F. Rios-Brito, and Ileana Cristina Rodriguez Vazquez are employees of Laboratorios Silanes.

Ethical Approval. This study was carried out entirely in accordance with the legal provisions of the General Health Law of the United

Mexican States and with the ethical principles emanating from the eighteenth World Medical Assembly in Helsinki, Finland, in 1964 and its respective amendments, concerning medical research on human beings. It was approved by the Research Ethics Committee of Investigación Biomédica para el Desarrollo de Fármacos S.A. de C.V. (Protocol approval number: CEI-000002). Study regulatory adherence: Ministry of Health in Mexico: Federal Commission for the Protection against Sanitary Risks (COFEPRIS) Approval Number: 223300410A0096/2021.

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