The Effect of a Losartan-Based Treatment Regimen on Isolated Systolic Hypertension

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This study was conducted to compare the antihypertensive efficacy and tolerability, over 12 weeks, of a losartan-based treatment regimen and placebo in patients with isolated systolic hypertension. Three hundred eight patients ≥35 years of age with isolated systolic hypertension, defined as trough sitting blood pressure between 140 and 200 mm Hg systolic and between 70 and 89 mm Hg diastolic, were randomized to losartan 50 mg (n=157) or placebo (n=151) once daily, with titration as necessary to achieve a goal trough sitting systolic blood pressure (SBP) <140 mm Hg. At baseline, mean trough sitting SBP was 140–159 mm Hg in 20.5% of patients, 160–179 mm Hg in 62.7%, and 180–200 mm Hg in 16.9%, and was similar in the two groups (losartan, 165.3 mm Hg; placebo, 166.1 mm Hg). At 12 weeks, mean trough sitting SBP decreased significantly (p<0.001) *in both the losartan-based treatment group (by 19.2 mm Hg) and in the placebo group (by 7.6 mm Hg). The reduction in sitting SBP was significantly greater for losartan than placebo (–11.6 mm Hg; 95% confidence interval, –14.8 to –8.4). In patients with isolated systolic hypertension, a once-daily losartan-based treatment regimen significantly lowered SBP. The losartan-based regimen exhibited antihypertensive efficacy that was superior to that of placebo, with a similar tolerability profile. (J Clin Hypertens. 2002;4:101–107)*

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Hypertension is one of the most common adult diseases in the United States, and is a well established risk factor for fatal and nonfatal cardiovascular and cerebrovascular events, including stroke, coronary heart disease, heart failure, and renal disease.[1] Historically, isolated systolic hypertension (ISH), defined in the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension as systolic blood pressure (SBP) ≥140 mm Hg with diastolic blood pressure (DBP) <90 mm Hg,[2] has been considered a less important gauge of cardiovascular health, and therefore has not been aggressively treated.[3] However, data from the Framingham Heart Study and other sources show that SBP is a better predictor of cardiovascular disease risk than DBP, especially for those over 60 years of age.[4–7]

ISH accounts for approximately two thirds of cases of hypertension among individuals greater than 60 years of age.[8] In Western countries, the prevalence of ISH increases precipitously, from 5% of 60-year-olds to 20% of octogenarians.[9] Therefore, improving outcomes in patients with hypertension requires the successful control of SBP, especially among elderly patients, in whom ISH is prevalent.

Several studies demonstrate that ISH is a modifiable cardiovascular risk factor.[10–12] In the Systolic Hypertension in the Elderly Program (SHEP),[11] 4736 patients with ISH were randomized to diuretic-based antihypertensive therapy or placebo for a mean of 4.5 years. Antihypertensive therapy reduced SBP as well as total mortality (–13%), fatal and nonfatal stroke (–36%), total cardiovascular events (–32%), and coronary heart disease events (–25%), compared with placebo.[10,11] Similarly, in the Systolic Hypertension in Europe Trial (Syst-Eur),[12] among 4695 patients with ISH followed for a medi-

an of 2 years, calcium channel blocker-based antihypertensive therapy reduced SBP as well as total mortality (–14%), fatal and nonfatal stroke (–42%), total cardiovascular events (–31%), and all cardiac events, including sudden death (–26%), compared with placebo.

ISH is thought to arise primarily from stiffening of the large arteries, with a resultant reduction in distensibility and elasticity.[13] The renin-angiotensin system-modulating medications, such as angiotensin II receptor antagonists (AIIAs, sometimes referred to as angiotensin II receptor blockers, or ARBs), can reduce arterial stiffness via several mechanisms.[14] Losartan has been shown to inhibit angiotensin II-mediated adverse vascular remodeling of the arterial wall and to normalize endothelial function of small arteries in patients with essential hypertension, effects that may render them useful in the treatment of ISH.[15] Losartan has been shown to be as effective as atenolol, amlodipine, nifedipine gastrointestinal therapeutic system, or enalapril in the reduction of SBP and DBP.[16–18] Its effects in ISH have not been extensively studied. In an open label, community-based trial, another AIIA was usually given in combination with hydrochlorothiazide (HCTZ) and was shown to reduce SBP in patients with ISH.[23] This paper reports the results of a multicenter, randomized, double-blind, placebo-controlled trial conducted to assess the efficacy and tolerability of a losartan-based regimen in the treatment of ISH. The primary hypothesis was that a once-daily losartan-based regimen is superior in antihypertensive efficacy to placebo in the treatment of patients with ISH after 12 weeks of therapy, as measured by the change from baseline in mean trough sitting SBP (SiSBP).

METHODS

Patients

Adults ≥35 years of age with ISH, defined as a mean trough SiSBP of 140–200 mm Hg and a mean trough sitting DBP (SiDBP) of 70–89 mm Hg were eligible for randomization into the study. Patients were excluded if they were taking more than two antihypertensive medications, their SiSBP varied by more than 15 mm Hg between the prerandomization and randomization visits, or if they had known or suspected secondary hypertension, a history of malignant hypertension, or clinically significant cardiovascular disease. Also excluded were patients with known sensitivity to an AIIA, hydrochlorothiazide, or any other sulfonamide-derived drugs; a history of angioedema, cerebrovascular disease, or syncopal disorder; unstable diabetes mellitus; severe hepatic impairment; a single functional kidney; moderate or severe renal impairment, as manifested by serum creatinine >1.5 mg/dL and creatinine clearance <40 mL/min (calculated by the Cockroft and Gault formula); proteinuria $>2^{+}$ by urine dipstick; anuria; serum potassium <3.5 or >5.5 mEq/L; hematuria (more than 20 red blood cells/high-power field or of unknown etiology); arm circumference >41 cm; or who were pregnant or breast-feeding. All patients provided written informed consent.

Procedures

The protocol for this multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial was approved by institutional review boards for the study sites. The study included a screening visit, a 2–4-week placebo run-in phase before which prestudy antihypertensive medications were discontinued if necessary, and a 12-week double-blind phase during which patients received a once-daily losartan-based treatment regimen or placebo.

Blood pressure was measured according to the American Heart Association recommendations,[19] using standard mercury sphygmomanometers. Patients rested quietly in the sitting position for 5 minutes before the first measurement of blood pressure and pulse rate. Mean readings were obtained by taking three consecutive sitting blood pressure readings separated by at least 1 minute, all of which had to be within ±5 mm Hg.

Screening. During the screening clinic visit, medical histories were obtained and a physical examination and 12-lead electrocardiography were performed. All clinical laboratory tests (complete blood cell count with differential, chem 7, alanine transaminase, aspartate transaminase, serum uric acid, and urinalysis) were performed in a central laboratory. After providing written informed consent, patients who were currently taking antihypertensive medications were instructed on procedures for discontinuing them before the 2–4-week placebo run-in phase.

Placebo Run-in Phase. Mean trough SiSBP and SiDBP were assessed at 2 and 4 weeks into the placebo run-in phase and at additional study visits scheduled at the investigator's discretion. Patients with a mean trough SiSBP <140 mm Hg or >200 mm Hg or a mean trough SiDBP ≥90 mm Hg were discontinued from the study. Patients with a mean trough SiSBP of 140–200 mm Hg and a mean trough SiDBP of 70–89 mm Hg could enter the double-blind phase of the study at the end of the 4-week washout period, or earlier if the investigator judged it appropriate and mean trough SiSBP was between 180 and 200 mm Hg on two study visits.

Double-Blind Treatment. For the 12-week double-blind treatment phase, patients were stratified by stage of ISH (stage 1, SiSBP 140–159 mm Hg; stage 2, 160–179 mm Hg; modified stage 3, 180–200 mm Hg) based on mean trough SiSBP at randomization. They were randomized to receive either a losartan-based regimen or placebo, to be taken once daily between 6 a.m. and 10 a.m.

Study visits occurred after 4, 8, and 12 weeks of treatment. During study visits, blood pressure and pulse measurements were obtained and adverse experiences (defined as any untoward medical occurrence regardless of its suspected cause) occurring since the last study visit were recorded. Blood pressure measurements were to be performed 22–26 hours after the last dose of study medication.

Concomitant therapy with any antihypertensive medication was prohibited. Additionally, concomitant therapy with lithium or other major psychotropic agents, oral steroids, or adrenocorticotropic hormone, or daily use of nonsteroidal anti-inflammatory drugs (NSAIDs) or high-dose aspirin was prohibited. Intermittent use of ephedrine, sildenafil, or NSAIDs was permitted, except within 72 hours of study visits.

If the SBP goal (<140 mm Hg) was not met at the week 4 study visit, losartan 50 mg was titrated to losartan 50 mg/HCTZ 12.5 mg once daily, with sham titration in the placebo group. If the SBP goal was not met at the week 8 study visit, patients who were taking losartan 50 mg received losartan 50 mg/HCTZ 12.5 mg once daily, while patients taking losartan 50 mg/HCTZ 12.5 mg received losartan 100 mg/HCTZ 25 mg once daily for the remaining 4 weeks of the study. The dose in the placebo group was sham titrated.

Patients whose mean trough SiSBP was 180–200 mm Hg at the time of the second titration received an additional blinded once-daily rescue treatment for the remainder of the study. Patients in the placebo group received blinded rescue treatment of losartan 50 mg, while those in the losartan-based treatment group received blinded placebo as rescue treatment. This approach was taken in order to provide rescue therapy for patients in the placebo group without unblinding patients in the losartan-based treatment group. Patients with a mean trough SiSBP of 200–220 mm Hg returned for repeat blood pressure measurements within 24 hours. At follow-up, if the mean trough SiSBP was >200 mm Hg, the patient was discontinued from the study. Patients with a mean trough SiSBP >220 mm Hg followed within 1 hour by a repeat measurement >200 mm Hg, and those with a mean trough SiDBP <60 or >100 mm Hg, were also discontinued.

Data Analysis

All patients taking study medication and having a valid mean SiSBP measurement at baseline and at least one valid measurement after baseline were included in the efficacy analyses. The primary efficacy measure was the mean change from baseline in trough SiSBP at week 12. Statistical analyses of the changes from baseline in SiSBP were conducted using the last-observation-carried-forward (LOCF) approach. Values obtained after initiation of rescue therapy in the placebo group were not used in the analysis but instead were imputed using LOCF of pre-rescue values. An analysis of covariance (ANCOVA) model was used to compare treatment groups; the model included terms for treatment and study site and baseline mean trough SiSBP as a covariate. Mean values presented in this report are least squares means, which are adjusted for the terms in the model. Mean changes in SiSBP from baseline to weeks 4 and 8, mean changes in SiDBP and pulse from baseline to weeks 4, 8, and 12, as well as post hoc analyses of mean changes in pulse pressure from baseline to weeks 4, 8, and 12 were also analyzed in this manner.

The percentages of patients who responded to treatment (i.e., reached the SBP goal of mean trough SiSBP of <140 mm Hg or at least a 20-mm Hg reduction from baseline in mean trough SiSBP) were compared between treatment groups using a logistic regression model, including terms for treatment and baseline SiSBP.

To assess the effect of the severity of hypertension at baseline on response to losartan, post hoc analyses of mean changes from baseline in mean trough SiSBP at week 12 were conducted by stage of ISH at randomization. Analysis of variance (ANOVA) models with terms for treatment, study site, stage of ISH, and treatment by stage interaction were used to compare treatments with respect to mean changes from baseline to week 12 in mean trough SiSBP. The study was not designed to detect differences between treatment groups within stages of ISH.

The safety of the treatment regimens was compared through Kaplan-Meier estimates of the cumulative incidences at week 12 of all adverse experiences (AEs) and drug-related AEs. The times to the first AE that occurred during the double-blind treatment period, but before the administration of rescue medication in the placebo group were used for these analyses.

Power calculations assumed a minimum detectable difference in SiSBP between the losartan-based treatment group and the placebo group of 8 mm Hg, with a standard deviation of 18 mm Hg. With 135 patients per treatment group, the study had 95% power to detect, at the 0.05 level with a two-sided test, an 8-mm Hg difference between

Table. Demographics, Clinical Characteristics, and Patient Disposition

	LOSARTAN (N=157)	PLACEBO (N=151)
Age in years, mean (SD)	66.9 (9.7)	66.7 (9.5)
Sex, no. (%)		
Male	71 (45.2)	72 (47.7)
Female	86 (54.8)	79 (52.3)
Race, no. (%)		
White	138 (87.9)	124 (82.1)
Black	7 (4.5)	17 (11.3)
Asian	2 (1.3)	1 (0.7)
Other	10 (6.4)	9 (6.0)
Baseline SiSBP (mm Hg), mean (SD)	165.3 (12.1)	166.1 (12.1)
Baseline SiDBP (mm Hg), mean (SD)	83.6 (5.4)	84.4 (5.6)
Baseline pulse pressure (mm Hg), mean (SD)	81.7 (12.7)	81.7 (12.8)
Baseline pulse rate (beats/min), mean (SD)	73.5 (8.7)	73.7 (8.3)
Stage of ISH*, no. (%)		
Stage 1: 140–160 mm Hg	32 (20.4)	31 (20.5)
Stage 2: 160–180 mm Hg	98 (62.4)	95 (62.9)
Modified stage 3: >180 mm Hg	27 (17.2)	25 (16.6)
Completed study, no. (%)	136 (86.6)	119 (78.8)
Discontinued study, no. (%)	21 (13.4)	32 (21.2)
Clinical adverse event	9 (5.7)	11 (7.3)
Withdrawn consent	1 (0.6)	7 (4.6)
Protocol deviation	3 (1.9)	2 (1.3)
Lost to follow-up	2 (1.3)	3 (2.0)
Lack of efficacy of study drug	2 (1.3)	3 (2.0)
Relocation	1 (0.6)	1 (0.7)
Laboratory adverse event	1 (0.6)	1 (0.7)
Other	2 (1.3)	4 (2.6)

SiSBP/DBP=sitting systolic/diastolic blood pressure; ISH=isolated systolic hypertension; *SiSBP values for stage 1, stage 2, and modified stage 3 are 140–159 mm Hg, 160–179 mm Hg, and 180–200 mm Hg, respectively.

losartan and placebo in the change from baseline in mean trough SiSBP.

RESULTS

Patients

The number of patients randomized to treatment was 308: 157 to the losartan-based treatment group and 151 to the placebo group. Demographic characteristics were similar between groups (Table). The majority of patients were white (85%) with a mean age of 66.8 years (range, 36–90 years). Approximately one half of patients (53.6%) were female.

Baseline clinical characteristics were comparable between groups (Table). The mean duration of ISH was 5.1 years (SD, 6.4). The majority of patients (62.7%) had stage 2 ISH, while 20.5% had stage 1 and 16.9% had modified stage 3. Twenty-one (13.4%) of the patients in the losartan-based treatment group and 32 (21.2%) of those in the placebo group prematurely discontinued, for reasons listed in the Table.

Use and Titration of Study Medication

At the week 4 visit, 25.2% (38/151) of patients in the losartan-based treatment group continued on losartan 50 mg and 14.3% (19/133) of patients in the placebo group continued on losartan 50 mg *placebo*. At this visit, 74.2% (112/151) of patients in the losartan-based treatment group were titrated to losartan 50 mg/HCTZ 12.5 mg and 0.7% (1/151) were titrated to losartan 100 mg/HCTZ 25 mg. Eighty-five percent (113/133) of patients in the placebo group were titrated to losartan 50 mg/HCTZ 12.5 mg placebo, and 0.8% (1/133) were titrated to losartan 100 mg/HCTZ 25 mg *placebo*. At the week 8 visit, 17.5% (25/143) of patients in the losartan-based treatment group continued on losartan 50 mg and 7.1% (9/126) of patients in the placebo group continued on losartan 50 mg *placebo*. At this visit, 34.3% (49/143) of patients in the

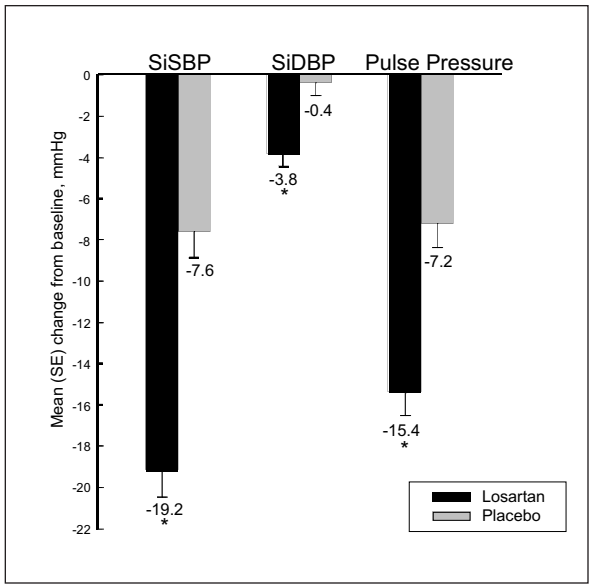

Figure 1. Mean change from baseline in sitting systolic blood pressure (SiSBP), sitting diastolic blood pressure (SiDBP), and pulse pressure after 12 weeks of treatment with a losartan-based treatment regimen or placebo
*p<*0.001 vs. placebo*

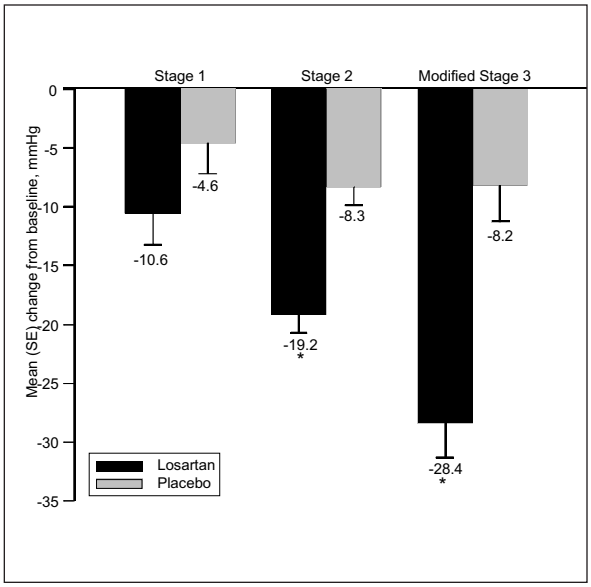

Figure 2. Mean change from baseline in sitting systolic blood pressure after 12 weeks of treatment with a losartan-based regimen or placebo by baseline severity of isolated systolic hypertension (stage 1=140–159 mm Hg; stage 2=160–179 mm Hg; modified stage 3=180–200 mm Hg)
*p<*0.001 vs. placebo*

losartan-based treatment group received losartan 50 mg/HCTZ 12.5 mg, and 18.3% (23/126) of patients in the placebo group received losartan 50 mg/HCTZ 12.5 mg *placebo*. At the week 8 visit, 43.4% (62/143) of patients in the losartan-based treatment group were titrated to losartan 100 mg/HCTZ 25 mg, and 61.9% (78/126) of patients in the placebo group were titrated to losartan 100 mg/HCTZ 25 mg *placebo*. At this visit, 4.9% (7/143) of patients in the losartan-based treatment group were given rescue medication, as were 12.7% (16/126) of patients in the placebo group. More than 95% of patients in both groups took at least 95% of their study medications.

The frequency of titration to higher doses of blinded study medication increased with the stage of ISH in both the losartan-based treatment group and the placebo group.

Trough SiSBP

As shown in the Table, mean baseline SiSBP was similar in the losartan-based treatment group (165.3 mm Hg) and the placebo group (166.1 mm Hg). For the LOCF analyses, there were 156, 155, 156, and 156 patients in the losartan-based treatment group at baseline and at weeks 4, 8, and 12, respectively, and 148 patients at baseline and at weeks 4, 8, and 12 in the placebo group. At weeks 4, 8, and 12, mean trough SiSBP decreased significantly ($p<0.001$) in both the losartan-based treatment and placebo groups. The differences between the treatment groups in mean changes from baseline systolic pressure were statistically significant ($p<0.001$) at each week. For the primary efficacy end point (week 12), the mean change from baseline systolic pressure was –19.2 mm Hg in the losartan-based treatment group, compared with –7.6 mm Hg in the placebo group ($p<0.001$) (Figure 1). Mean changes at week 4 and week 8 were –12.9 mm Hg and –19.2 mm Hg in the losartan-based treatment group and –5.8 mm Hg and –7.5 mm Hg in the placebo group. The differences between the groups were –7.1 mm Hg (95% confidential interval [CI], –10.0 to –4.2) at week 4 (losartan as monotherapy minus placebo); –11.7 mm Hg (95% CI, –15.1 to –8.3) at week 8 (losartan with or without HCTZ minus placebo); and –11.6 mm Hg (95% CI, –14.8 to –8.4) at week 12 (losartan with or without HCTZ minus placebo).

Percentage of Patients Responding to Therapy

The percentage of patients responding to treatment (i.e., trough SiSBP <140 mm Hg or at least a 20-mm Hg decrease from baseline if mean trough value was >140 mm Hg) was significantly higher in the losartan-based treatment group than in the placebo group at the end of the study ($p<0.001$). At study end (week 12), 54% (85/156) of patients in the losartan-based treatment group, compared with 28% (42/148) of placebo patients, had responded. The odds (and 95% CI) of responding to treatment were 3.02 (1.87–4.86) times greater with losartan than with placebo ($p<0.001$).

Effect of Baseline Hypertension Stage on Antihypertensive Efficacy

For all stages of baseline hypertension, after 12 weeks of treatment, a losartan-based regimen was more effective than placebo at lowering mean SiSBP. Statistical significance ($p<0.001$) was achieved for stage 2 and modified stage 3 hypertension (Figure 2).

Trough SiDBP

As shown in the Table, mean baseline SiDBP was similar in the losartan-based treatment group (83.6 mm Hg) and the placebo group (84.4 mm Hg). Mean trough SiDBP decreased significantly ($p<0.001$) in the losartan-based treatment group, by 2.5, 4.4, and 3.8 mm Hg at weeks 4, 8, and 12, respectively, but not in the placebo group (Figure 1). The differences between the treatment groups with respect to changes from baseline were significant at each week. The difference (losartan minus placebo) was –2.4 mm Hg (95% CI, –3.8 to –1.1) at week 4; –3.6 mm Hg (95% CI, –5.1 to –2.0) at week 8; and –3.4 mm Hg (95% CI, –5.0 to –1.9) at week 12.

Pulse Pressure

Mean baseline pulse pressure was 81.7 mm Hg in both treatment groups. Mean trough pulse pressure decreased significantly ($p<0.001$) in the losartan-based treatment group by 10.4, 14.8, and 15.4 mm Hg at weeks 4, 8, and 12, respectively, and decreased significantly ($p<0.001$) in the placebo group by 5.8, 6.6, and 7.2 mm Hg at weeks 4, 8, and 12 (Figure 1). The differences between the treatment groups with respect to changes from baseline were significant ($p\leq0.001$) at each week. The difference (losartan minus placebo) was –4.6 mm Hg (95% CI, –7.3 to –1.9) at week 4, –8.1 mm Hg (95% CI, –11.0 to –5.2) at week 8, and –8.1 mm Hg (95% CI, –11.0 to –5.3) at week 12.

Pulse Rate

Baseline sitting pulse rate was 73.5 beats/min in the losartan-based treatment group and 73.7 beats/min in the placebo group. No significant changes from baseline were observed for either group at any time point, nor were the mean changes from baseline significantly different between the two groups at any week.

Clinical and Laboratory AEs

Similar proportions of patients in both groups reported at least one AE: 49.7% (78/157) of losartan patients and 53.0% (80/151) of placebo patients. Kaplan-Meier estimates of the percentage of patients in each treatment group who experienced at least one clinical AE by study end were 50.5% (95% CI, 42.5%, 58.5%) for patients in the losartan-based treatment group and 55.2% (95% CI, 46.8%, 63.6%) for patients in the placebo group. Drug-related clinical AEs were reported by 10.4% of patients, 12.7% (20/157) of those in the losartan-based treatment group and 7.9% (12/151) of those in the placebo group. Kaplan-Meier estimates of the percentage of patients in each treatment group who experienced at least one drug-related clinical AE by study end were 13.4% (95% CI, 7.9%, 18.8%) for patients in the losartan-based treatment group and 9.0% (95% CI, 3.8%, 14.2%) for patients in the placebo group.

Similar proportions of patients in both the losartan-based treatment group and placebo group reported the most common AEs, which included upper respiratory infection (7.6% losartan; 8.6% placebo), headache (5.1% losartan; 7.3% placebo), dizziness (5.7% losartan; 2.6% placebo), sinusitis (4.5% losartan; 2.0% placebo), lower extremity edema (1.9% losartan; 3.3% placebo), urinary tract infection (3.2% losartan; 0.7% placebo), and diarrhea (3.2% losartan; 0% placebo). No other AEs were reported by >3% of patients in either group. No clinically significant changes in laboratory tests were observed.

DISCUSSION

In this study, the first large, prospective, placebo-controlled trial of an AIIA in the treatment of ISH, a once-daily losartan-based treatment regimen was consistently more effective than placebo at reducing SBP in patients with ISH. The effect of the losartan-based treatment regimen was observed beginning with the first blood pressure measurement at week 4 and was maintained throughout the 12-week treatment period. At week 12, the placebo-adjusted mean change from baseline in trough SiSBP was –11.6 mm Hg. Comparable placebo-adjusted reductions in SiSBP were observed in the SHEP and Syst-Eur studies. In SHEP[11] and Syst-Eur,[12] the mean differences in SiSBP reduction between the active and placebo groups were 10–11 mm Hg, with achieved mean SiSBP of 144 mm Hg and 151 mm Hg, respectively, in the actively treated groups. The current study was not designed to determine the impact of treatment of ISH with a losartan-based regimen on cardiovascular morbidity and mortality.

The data from this study extend those of a randomized, double-blind comparison of losartan and atenolol in the treatment of ISH.[20] In that study, patients received losartan 50 mg or atenolol 50 mg once daily over a 16-week treatment period with HCTZ added at weeks 8 and 12 if necessary. Both the losar-

tan and atenolol-based regimens effectively reduced baseline SiSBP in patients with ISH (173.7 mm Hg reduced to 149.0 mm Hg with losartan and 173.5 mm Hg reduced to 148.2 mm Hg with atenolol).

In the current study, as expected, patients with advanced stages of ISH required higher doses of study therapy to attain blood pressure control. This finding is consistent with the experience of other large clinical trials attempting to achieve an SBP of <140 mm Hg, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[21] and the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) study.[22] In the current study, the tolerability profile of the losartan-based regimen in the treatment of ISH was similar to that of placebo, as indicated by the incidence of any AEs and of drug-related AEs.

CONCLUSION

In patients with ISH, a once-daily losartan-based treatment regimen significantly lowered SBP. The losartan-based regimen exhibited antihypertensive efficacy that was superior to that of placebo, with a similar tolerability profile.

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