ORIGINAL ARTICLE

Comparison of 24-Hour Ambulatory Central Blood Pressure Reduction Efficacy Between Fixed Amlodipine or Up-Titrated Hydrochlorothiazide Plus Losartan: The K-Central Study

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OBJECTIVE

The main objective of this study was to evaluate non-inferiority of office mean systolic blood pressure (BP) reduction efficacy and superiority of 24-hour ambulatory central BP reduction efficacy between losartan combined with fixed dose amlodipine (L/A group) and dose up-titrated hydrochlorothiazide (L/H group) according to office BP.

METHODS

We conducted a prospective, randomized, double-blind multicenter trial in 231 patients with hypertensive (mean age = 59.2 ± 12.2 years). Patients received losartan 50 mg monotherapy for 4 weeks, followed by additional use of amlodipine 5 mg or hydrochlorothiazide 12.5 mg for 20 weeks after randomization. The patients who did not achieve the BP goal after 4 weeks'

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randomization received an increased dose of 100 mg/5 mg for the L/A group and 100 mg/25 mg for L/H group, respectively. The 24-hour ambulatory central BP was measured at baseline and after 20 weeks' treatment.

RESULTS

Office mean systolic BP reduction of L/A group was not inferior to L/H group after 4 weeks' treatment (−17.6 ± 13.3 vs. −14.4 ± 12.6 mm Hg, $P = 0.0863$) and was not significantly different after 20 weeks' treatment. (−15.7 ± 14.0 vs. −14.7 ± 15.1 mm Hg, $P = 0.6130$) The 24-hour ambulatory central systolic BP was significantly more reduced in the L/A group compared with that in the L/H group after 20 weeks' treatment (−9.37 ± 10.67 vs. −6.28 ± 10.50 mm Hg, $P = 0.0407$). The 24-hour ambulatory central systolic BP at the completion of the study and its reduction magnitude were independently associated with reductions in aortic pulse wave velocity, pulse pressure, and wave reflection magnitude.

CONCLUSION

Office systolic BP reduction with L/A was not inferior to L/H after 4 week's treatment. The combination of losartan and amlodipine was more favorable in 24-hour ambulatory central hemodynamics beyond BP-lowering efficacy than the combination of losartan and hydrochlorothiazide, regardless of office BP.

CLINICAL TRIALS REGISTRATION

NCT02294539

Keywords: amlodipine; blood pressure; combination; central blood pressure; hydrochlorothiazide; hypertension; losartan

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The guidelines on the management of arterial hypertension have begun to highlight the importance of assessing total cardiovascular risk and quantification of subclinical target organ damage in the management of hypertensive patients since 2003.[1] Central pressures are more relevant than peripheral pressures in the pathogenesis of cardiovascular disease[2,3] and may have predictive value independent of the corresponding peripheral blood pressure (BP). Large-scale trials have shown that central hemodynamics may provide a worthwhile treatment target.[4–9] Therefore, antihypertensive therapy beyond BP-lowering effect, reducing central BP, has been regarded as promising in cardiovascular mortality reduction.

Previous studies showed that a calcium channel blocker (CCB) combined with angiotensin-converting enzyme inhibitor (ACEI) was more efficacious on central BP reduction compared with diuretics with β-blocker.[10] The heart rate-lowering effect of a β-blocker might unfavorably affect the central BP in this study. Other studies revealed that fixed-dose angiotensin receptor blocker (ARB) and CCB, azelnidipine 16 mg, combination therapy is favorable in reducing central BP compared with same-dose ARB plus diuretics, hydrochlorothiazide 12.5 mg.[11] However, the efficacy of 12.5 mg hydrochlorothiazide was not comparable with that of azelnidipine 16 mg, because azelnidipine-based therapy showed greater mean arterial pressure reduction in this study. Meanwhile, recently published data revealed that hydrochlorothiazide monotherapy is not inferior to CCB monotherapy in improving central BP.[12] Therefore, it is necessary to compare central BP reduction efficacy between commonly prescribed combination drugs with comparable classes and permissible dose.

The Mobil-O-Graph BP device provides oscillometric noninvasive estimation of 24-hour central BP and as is similarly effective as the well-established SphygmoCor applanation tonometry device. It measures 24-hour brachial and central BPs within 1 measurement.[13] It is the first automated device that uses brachial oscillometric BP for a noninvasive estimation of the central BP within 1 measurement.

We hypothesize that losartan plus amlodipine (most widely prescribed CCB)[14] is not inferior to losartan plus hydrochlorothiazide (most widely prescribed thiazide-type diuretics)[14,15] in reduction of office mean systolic BP after 4-week treatment and superior to 24-hour ambulatory central BP reduction efficacy after 20-week treatment.

METHODS

Study design and subjects

This is a multicenter, double-blind, active-controlled, randomized trial with 2 treatment arms comparing the efficacy on 24-hour central BP reduction. From August 2014 to May 2016, patients with hypertension were recruited from 18 university hospitals in 8 cities via outpatient departments. Both hypertension-naïve patients and known patients with hypertension were recruited. Losartan 50 mg monotherapy was performed in the 4-week run-in period to wash out the effects of previous antihypertensive drugs. After 4 weeks of run-in period, the subjects whose systolic BP was ≥140 mm Hg were enrolled in the study. Inclusion and exclusion criteria were described in our publication on the study design previously.[16] Men and women from ages 19 to 80 years, with history of hypertension or those newly diagnosed with a systolic BP ≥ 140 mm Hg, are to be included in the study. The exclusion criteria are (i) mean sitting diastolic BP ≥ 110 mm Hg or mean sitting systolic BP ≥ 180 mm Hg at screening or randomization; (ii) variability of ≥20 mm Hg in systolic BP or ≥10 mm Hg in diastolic BP between 3 measurements, or differences of ≥20/10 mm Hg in left-to-right brachial values of systolic BP or diastolic BP; (iii) secondary hypertension; (iv) malignant hypertension; (v) allergies or contraindications to ARB, CCB, or sulfonamides; (vi) uncontrolled diabetes mellitus (HbA1c ≥ 10%); (vii) history of New York Heart Association class III–IV heart failure, angina, myocardial infarction, cardiomyopathy, arrhythmia, or aortic stenosis requiring treatment within 6 months; (viii) cerebral vascular disease within 6 months; (ix) serious liver or renal dysfunction; (x) symptomatic hyperuricemia or gout; (xi) galactose or lactose intolerance; (xii) patients with diabetes or moderate-to-severe renal dysfunction on drugs containing aliskiren; (xiii) pregnancy or the possibility of pregnancy, or breast feeding; (xiv) unable to withhold current medication; (xv) prescription of other study drugs within 4 weeks; and (xvi) abnormal laboratory results (aspartate aminotransferase, alanine transaminase > 3 upper

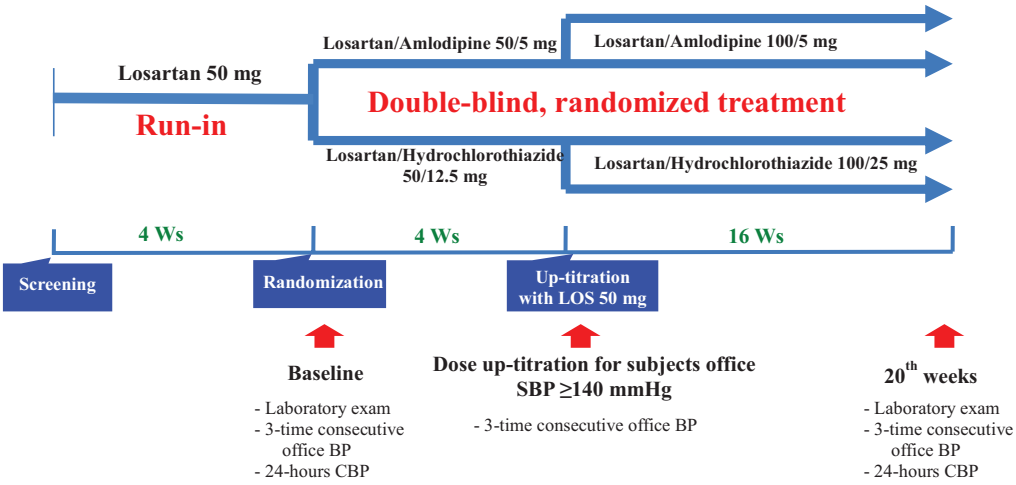

Figure 1. Study design of multicenter, double-blind, active-controlled, randomized trial with two treatment arms. Both losartan 50 mg plus amlodipine 5 mg combination arm and losartan 50 mg plus hydrochlorothiazide 12.5 mg combination arm were dose up-titrated to losartan 100 mg, with the same dose of amlodipine (5 mg) or hydrochlorothiazide 25 mg, respectively, in case of failure to achieve the blood pressure (BP) goal (mean sitting systolic BP ≥ 140 mm Hg) after 4 weeks of combination therapy. At the baseline and study completion, office brachial BP, 24-hour central BP, 24-hour aortic pulse wave velocity, and other 24-hour hemodynamic parameters were measured using the Mobil-O-Graph device. Blood and urine tests were performed at the baseline and end of the study.

limit of normal, Cr >2.0 mg/dL, K^+ <3.5 or >5.5 mEq/L, Na^+ <125 mEq/L, Protein >2+ on dipstick, or protein/creatinine >1,000 mg/g on spot urine).

Both losartan 50 mg plus amlodipine 5 mg (L/A) and plus hydrochlorothiazide 12.5 mg (L/H) combination arms were up-titrated to losartan 100 mg, with same dose of amlodipine (5 mg) or hydrochlorothiazide 25 mg at the same time when the patients failed to achieve the office BP goal (mean sitting systolic BP ≥ 140 mm Hg) after the 4-week combination therapy (Figure 1).

We have educated patients to take their medications after breakfast and prohibited patients from taking any antihypertensive medication other than the study medications. Other drugs that might interfere with the safety and efficacy of the study medications were also not allowed. At the baseline and completion of the study, office brachial BP, pulse pressure, central BP, 24-hour aortic pulse wave velocity (aPWV), and other 24-hour hemodynamic parameters such as augmentation index at heart rate of 75 bpm (AI@75), and reflection magnitude (RM) were measured using the Mobil-O-Graph device. Blood and urine tests were performed as described in a previous publication about the study design and methods.[16]

This study was conducted in accordance with the Declaration of Helsinki. All investigators obtained approval from the institutional review boards of each participating center. All subjects signed a written consent form approved by the institutional review board. The study was also in accordance with the Korean Good Clinical Practice and International Conference on Harmonization-Good Clinical Practice (Clinicaltrials.gov Identifier: NCT02294539).

Office BP measurements

Office BP measurements were obtained in the sitting position with the pressure cuff placed at either the right or left brachial area using a semiautomated sphygmomanometer (HEM-7080IC, Omron Healthcare Co, Kyoto, Japan). After a 5-minute rest, BPs were measured 3 times with a 2-minute interval. We chose the arm with higher BP, and mean pressure was used in the analysis. If the BP differences between both arms were more than 20 mm Hg, the patients failed the randomization.

24-hour ambulatory central pressure monitoring

Ambulatory measurements of central BP, aPWV, AI@75, and wave RM were performed using a previously validated, automated oscillometric device (Mobil-O-Graph 24-hour PWA monitor; I.E.M. Gmbh, Stolberg, Germany).[17–20] The setting of measurements was every 30 minutes, and the patients with valid data of more than 90% in the 24-hour measurement were included in the analysis.

Statistical analysis

Study sample size and efficacy evaluation were described in a previous publication.[16]

Statistical analysis was performed per protocol. Intergroup comparison was analyzed with 2-sample *t*-test, and baseline to 4-week or baseline to 20-week differences were evaluated with paired *t*-test for continuous variables. Chi-square test was used for comparison of categorical variables. For the evaluation of independent factors that are related to central BP reduction, multiple regressions with stepwise analysis were conducted. Two-sided values of $P < 0.05$ indicate statistical significance. All statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc.).

Outcome measures

The outcome was the (i) noninferiority comparison of losartan 50 mg/amlodipine 5 mg combination with losartan

50 mg/hydrochlorothiazide 12.5 mg on office systolic BP after 4 weeks' treatment and (ii) superiority comparison between L/A and L/H groups on central BP after 20 weeks' treatment.

To demonstrate noninferiority the 2-sided 95% confidence interval (CI) had to be entirely above the predefined noninferiority margin of delta, –3 mm Hg.[17,18]

RESULTS

Baseline characteristics and laboratory data

A total of 368 patients with hypertension were screened. Among these patients, 231 were randomized to the study, except for 100 patients who failed to attain an office systolic BP of ≥140 mm Hg after 4 weeks of losartan monotherapy, 28 patients who withdrew their consent and 9 patients who failed to enrollment because of the protocol violation, pregnancy, and take medication that prohibited. After randomization, 44 patients were excluded because the number of measurements from the 24-hour Mobile-O-Graph examinations was not adequate for the analysis. Finally, 187 patients who completed the 24-hour Mobile-O-Graph examination were analyzed for per-protocol set.

The mean age of participants was 59.2 ± 12.2 years, and a total of 132 (70.6%) male patients were included (Table 1). There were no significant differences in baseline characteristics, classes of previous antihypertensive medications, and current medical history with laboratory data except the uric acid level of participants. On the study completion, serum uric acid level was equalized between 2 groups, and serum fasting glucose ($P = 0.0321$) and $HbA1_C$ ($P = 0.0071$) levels were lower in the losartan/amlodipine group compared with those in the losartan/hydrochlorothiazide group. The patients with up-titrated dose and the patients for whom the existing combination dosage was maintained were compared with respect to their number, BP, and other characteristics. The findings have been presented in Supplementary Tables 1–4. Supplementary Table 5 shows the office BP data of these unregistered patients whose systolic BP decreased to <140 mm Hg after losartan monotherapy.

The Na^+ level was significantly lower in the losartan/hydrochlorothiazide group ($P = 0.0037$) after the 20-week treatment. There was no significant difference in the serum K^+ level between the 2 groups (Tables 1 and 2).

Changes in office BP and 24-hour ambulatory BP

Baseline office BP measurements showed no significant differences in systolic, diastolic, and mean arterial pressure between groups. Moreover, pulse pressure (PP) and heart

Table 1. Baseline characteristics

	L/A (*n* = 92)	L/H (*n* = 95)	Total (*n* = 187)	*P* value
Male, *n* (%)	71 (77.2)	61 (64.2)	132 (70.6)	0.0518
Age, years	59.2 ± 12.4	59.2 ± 12.0	59.2 ± 12.2	0.9972
Height, cm	165.8 ± 8.5	164.4 ± 9.3	165.1 ± 8.9	0.2979
Weight, kg	70.9 ± 11.6	70.1 ± 11. 2	70.5 ± 11.4	0.6563
Waist circumference, cm	88.8 ± 8.6	89.3 ± 9.6	89.1 ± 9.1	0.6802
Renin–angiotensin–aldosterone blockers, *n* (%)	49 (53.3)	63 (66.3)	112 (59.9)	0.0686
β-blockers, *n* (%)	11 (12.0)	7 (7.4)	18 (9.6)	0.2876
Calcium channel blockers, *n* (%)	26 (28.3)	22 (23.2)	48 (25.7)	0.4245
Diuretics, *n* (%)	4 (4.3)	7 (7.4)	11 (5.9)	0.3801
Lipid-lowering agents, *n* (%)	35 (38.0)	36 (37.9)	71 (38.0)	0.9833
Medical history				
Diabetes mellitus, *n* (%)	11 (12.0)	19 (20.0)	30 (16.0)	0.1340
Dyslipidemia, *n* (%)	41 (44.6)	47 (49.5)	88 (47.1)	0.5014
Alcohol drinking				0.6089
Present drinker, *n* (%)	47 (51.1)	55 (57.9)	102 (54.5)	
Past drinker, *n* (%)	8 (8.7)	6 (6.3)	14 (7.5)	
Nondrinker, *n* (%)	37 (40.2)	34 (35.8)	71(38.0)	
Tobacco smoking				0.6279
Present smoker, *n* (%)	18 (19.6)	21 (22.1)	39 (20.9)	
Ex-smoker, *n* (%)	28 (30.4)	23 (24.2)	51 (27.3)	
Nonsmoker, *n* (%)	46 (50.0)	51 (53.7)	97 (51.9)	

Abbreviations: L/A, losartan (50 or 100 mg) and amlodipine (5 mg) combination; L/H, losartan (50 or 100 mg) and hydrochlorothiazide (12.5 or 25 mg) combination.

Table 2. Laboratory data

	Baseline			20-week treatment		
	L/A	L/H	*P* value	L/A	L/H	*P* value
Glucose (mg/dL)	106.4 ± 18.9	108.8 ± 17.1	0.3630	108.0 ± 17.5	115.3 ± 27.7	0.0321
BUN (mg/dL)	14.1 ± 3.4	14.5 ± 4.0	0.5225	15.4 ± 4.3	15.8 ± 4.5	0.5079
Creatinine (mg/dL)	0.90 ± 0.18	0.86 ± 0.20	0.1858	0.89 ± 0.20	0.88 ± 0.21	0.7579
Uric acid (mg/dL)	5.8 ± 1.3	5.4 ± 1.4	0.0478	5.6 ± 1.4	5.9 ± 1.6	0.1777
Total cholesterol (mg/dL)	184.5 ± 37.2	189.0 ± 36.7	0.4139	182.4 ± 35.7	188.9 ± 37.0	0.2281
HbA1c (%)	5.8 ± 0.8	5.9 ± 0.7	0.3607	5.7 ± 0.6	6.0 ± 1.0	0.0071
Sodium (mmol/L)	140.8 ± 2.0	141.1 ± 2.2	0.3069	141.0 ± 2.5	140.0 ± 2.1	0.0037
Potassium (K) (mmol/L)	4.4 ± 0.3	4.4 ± 0.3	0.9417	4.3 ± 0.3	4.3 ± 0.4	0.3401
CRP (mg/dL)	0.5 ± 1.3	0.3 ± 0.6	0.2611	0.4 ± 0.9	0.4 ± 0.6	0.8458
Albumin/creatinine (μg/mg)	24.0 ± 43.0	31.1 ± 83.5	0.4875	21.6 ± 37.1	21.8 ± 29.0	0.9641

Abbreviations: BUN, blood urea nitrogen; CRP, C-reactive protein; L/A, losartan (50 or 100 mg) and amlodipine (5 mg) combination; L/H, losartan (50 or 100 mg) and hydrochlorothiazide (12.5 or 25 mg) combination.

rate showed no significant differences. After the 4-week treatment before up-titration of combination drugs, the office systolic (136.1 ± 14.2 vs. 139.3 ± 13.8, $P = 0.1131$) and diastolic BPs (82.4 ± 9.3 vs. 84.1 ± 11.0, $P = 0.2455$) and their reduction magnitudes (–17.6 ± 13.3 vs. –14.4 ± 12.6, $P = 0.0863$ for systolic BP reduction and –9.9 ± 7.6 vs. –8.3 ± 8.3, $P = 0.1651$ for diastolic BP reduction) were not significantly different. As a primary endpoint of the study, the differences in systolic BP reduction between groups after the 4-week treatment were –3.2620 mm Hg (95% [CI] = –6.9942 to 0.4701) suggestive of noninferiority of office systolic BP reduction efficacy of the L/A group compared with L/H group (Table 3). Furthermore, after 20-week treatment, there were no significant differences in systolic, diastolic, and mean BPs between the 2 groups on office BP measurements (Table 3). There were no significant differences in 24-hour ambulatory systolic and diastolic BP monitoring at baseline and after 20-week treatment between groups. The reduction magnitude of 24-hour ambulatory SBP was significantly greater in L/A group ($P = 0.0411$; Table 3).

Changes in 24-hour ambulatory central BP and hemodynamic parameters

The 24-hour ambulatory central BP measurements showed no significant differences in baseline systolic and diastolic pressures between groups. After the 20-week treatment, the 24-hour ambulatory central systolic BP in losartan/amlodipine group was significantly more reduced compared with that in the losartan/hydrochlorothiazide group (–9.37 ± 10.67 vs. –6.28 ± 10.50 mm Hg, $P = 0.0407$, differences between means = –3.0854 mm Hg, 95% CI = –6.1397 to –0.0310; Table 3; Figure 2A). The 24-hour measurements of AI@75 were not significantly different between the 2 groups on baseline and after the 20-week treatment. However, the PP in the 24-hour measurement was significantly lower in the losartan/amlodipine group compared with that in the losartan/hydrochlorothiazide group (45.4 ± 8.1 vs. 48.0 ± 8.3 mm Hg, $P = 0.0342$; Table 3). The PP (–4.2 ± 5.7 vs. –1.4 ± 6.9 mm Hg $P = 0.0025$), aPWV (–0.3 ± 0.4 vs. –0.1 ± 0.4 m/s, $P = 0.0323$), and RM (–0.8 ± 3.6 vs. 0.4 ± 3.9, $P = 0.0285$) in the 24-hour measurement showed significantly greater reduction in the losartan/amlodipine group compared with those in the losartan/hydrochlorothiazide group (Table 3; Figure 2B).

Factors associated with central BP reduction

On regression analysis, 24-hour ambulatory central systolic BP and its reduction magnitude from baseline to 20 weeks' treatment in this study were independently associated with age, aPWV, PP, and wave RM at the end of the study (Table 4). We applied all suggestive factors that known to affect central BP including age, office BP, and 24-hour ambulatory BP data to univariate analysis (Supplementary Tables 6 and 8) Also, gender factors were included because of male predominance of the participants. In the multivariate regression analysis, the difference found in the degree of 24-hour central BP remission between the 2 groups had no correlation with the decrease in the office SBP, 24-hour ambulatory SBP, and gender but did correlate with the level of aPWV, RM, and PP after 20 weeks of treatment (Table 4 and Supplementary Tables 6–10). The study was designed to control the office BP to be at almost at the same level to minimize the influence of office BP remission on central BP remission.

DISCUSSION

This study results revealed that losartan plus amlodipine therapy was not inferior to losartan plus hydrochlorothiazide therapy on office systolic BP reduction after 4 weeks' treatment and had a more beneficial effect on 24-hour central systolic BP reduction after 20 weeks' treatment. The 24-hour ambulatory central systolic BP at the study completion and its reduction magnitude from baseline to 20 weeks' treatment

Table 3. Office blood pressure (BP) and 24-hour ambulatory central hemodynamic data

		Baseline			4-week treatment			Differences between baseline and 4-week treatment			20-week treatment			Differences between baseline and 20-week treatment		
		L/A (*n* = 92)	L/H (*n* = 95)	*P* value	L/A (*n* = 92)	L/H (*n* = 95)	*P* value	L/A (*n* = 92)	L/H (*n* = 95)	*P* value	L/A (*n* = 92)	L/H (*n* = 95)	*P* value	L/A (*n* = 92)	L/H (*n* = 95)	*P* value
Office BP	Systolic (mm Hg)	153.7 ± 10.9	153.7 ± 9.5	0.9984	136.0 ± 14.2	139.3 ± 13.8	0.1131	–17.6 ± 13.3	–14.4 ± 12.6	0.0863	138.0 ± 13.1	139.0 ± 13.3	0.5761	–15.7 ± 14.0	–14.7 ± 15.1	0.6130*
	Diastolic (mm Hg)	92.3 ± 9.0	92.4 ± 8.0	0.9287	82.4 ± 9.3	84.1 ± 11.0	0.2455	–9.9 ± 7.6	–8.3 ± 8.3	0.1651	83.0 ± 9.4	85.2 ± 10.1	0.1183	–9.3 ± 7.8	–7.2 ± 8.0	0.0666
	Mean arterial (mm Hg)	112.7 ± 7.9	112.8 ± 6.5	0.9434	100.3 ± 10.0	102.5 ± 11.0	0.1446	–12.5 ± 8.9	–10.3 ± 9.1	0.1011	101.3 ± 9.4	103.2 ± 10.0	0.1923	–11.5 ± 9.4	–9.7 ± 9.8	0.2063
	Pulse pressure (mm Hg)	61.4 ± 11.7	61.3 ± 11.7	0.9496	53.7 ± 10.8	55.2 ± 10.4	0.3263	–7.8 ± 9.1	–6.1 ± 8.4	0.2034	55.0 ± 11.3	53.8 ± 11.1	0.4773	–6.4 ± 9.0	–7.5 ± 9.9	0.4478
	Heart rate (bpm)	70.6 ± 10.9	71.7 ± 11.0	0.4788	73.5 ± 10.1	75.8 ± 10.6	0.1214	2.9 ± 8.5	4.1 ± 10.0	0.3612	73.5 ± 10.9	72.8 ± 10.1	0.6679	3.0 ± 8.9	1.2 ± 9.6	0.1860
24-hour am brachial BP	Systolic (mm Hg)	136.7 ± 12.5	136.6 ± 10.5	0.9752	—	—	—	—	—	—	126.6 ± 11.3	130.0 ± 12.4	0.0506	–10.1 ± 11.9	–6.7 ± 10.8	0.0411
	Diastolic (mm Hg)	87.1 ± 9.9	87.3 ± 9.2	0.8880	—	—	—	—	—	—	81.1 ± 8.7	82.1 ± 9.5	0.4707	–6.0 ± 8.2	–5.2 ± 7.8	0.5320
24-hour am central BP	Systolic (mm Hg)	126.9 ± 11.9	126.2 ± 9.9	0.6655	—	—	—	—	—	—	117.5 ± 10.1	119.9 ± 11.2	0.1261	–9.4 ± 10.7	–6.3 ± 10.5	0.0407**
	Diastolic (mm Hg)	88.3 ± 10.3	88.8 ± 9.7	0.7296	—	—	—	—	—	—	82.5 ± 8.9	83.4 ± 10.0	0.5272	–5.8 ± 8.3	–5.5 ± 8.1	0.7705
24-hour am hemodynamic parameters	aPWV (m/s)	9.0 ± 1.7	8.9 ± 1.7	0.8491	—	—	—	—	—	—	8.7 ± 1.6	8.8 ± 1.7	0.7437	–0.3 ± 0.4	–0.1 ± 0.4	0.0323
	AI@75 (%)	24.8 ± 7.9	25.8 ± 7.8	0.3991	—	—	—	—	—	—	23.8 ± 7.6	25.0 ± 7.6	0.3420	–1.0 ± 5.4	–0.7 ± 5.4	0.7687
	RM (%)	65.7 ± 4.2	65.1 ± 4.7	0.3331	—	—	—	—	—	—	64.9 ± 5.1	65.5 ± 5.0	0.4619	–0.8 ± 3.6	0.4 ± 3.9	0.0285
	PP (mm Hg)	49.7 ± 8.7	49.4 ± 8.8	0.8184	—	—	—	—	—	—	45.4 ± 8.1	48.0 ± 8.3	0.0342	–4.2 ± 5.7	–1.4 ± 6.9	0.0025

Abbreviations: Am, ambulatory; aPWV, aortic pulse wave velocity; AI@75, augmentation index at heart rate of 75 bpm; BP, blood pressure; L/A, losartan (50 or 100 mg) and amlodipine (5 mg) combination; L/H, losartan (50 or 100 mg) and hydrochlorothiazide (12.5 or 25 mg) combination; RM, wave reflection magnitude.

*Differences between means = –1.0794 mm Hg, 95% confidence interval = –5.2820 to 3.1232.

**Differences between means = –3.0854 mm Hg, 95% confidence interval = –6.1397 to –0.0310.

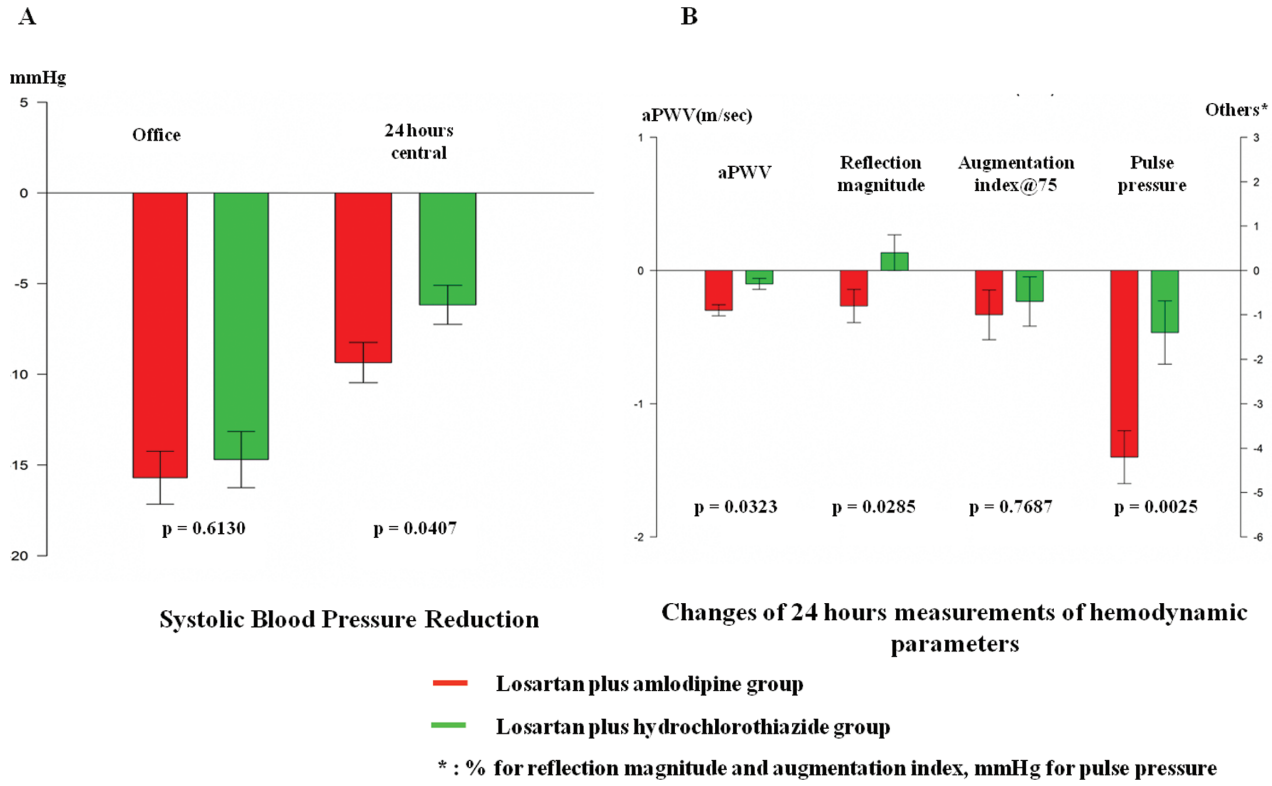

Figure 2. Bar graph shows changes in office systolic blood pressure (BP) and 24-hour ambulatory central systolic BP in the two groups (**a**) and 24-hour measured aortic pulse wave velocity (aPWV) (m/s), AI@75 (%), and reflection magnitude of wave (%) in the two groups (**b**). There are significant differences in reduction of 24-hour central systolic BP between groups (a). Moreover, there are significantly greater reductions in aPWV and wave reflection magnitude in losartan plus amlodipine combination group compared with that in losartan plus hydrochlorothiazide group.

were independently associated with reductions in aPWV, PP, and wave RM. This study was designed to compare fixed-dose amlodipine (5 mg) combination vs. up-titrated hydrochlorothiazide (12.5–25 mg) combination according to whether or not target BP achievement after 4 weeks' treatment, because preceded study, in which the mean arterial pressure of ARB plus CCB arm was lower than ARB plus diuretics arm, showed CCB combination was beneficial to reducing central BP.[11] The subjects of this study happened to be young (mean age 59 years; Table 1) and had no advantage from diuretics. As a result, there were no significant differences in reduction of office BP and mean arterial pressure after 20 weeks' treatment between groups (Table 3) and we could minimize the influence of office BP remission on central BP remission. Therefore, the combination of losartan and amlodipine was more favorable in central hemodynamics beyond BP-lowering efficacy than the combination of losartan and hydrochlorothiazide, regardless of office BP reduction.

In this study, we measured the 24-hour averaged central BP and hemodynamic parameters using a validated oscillometric noninvasive technique[19–26] by which we predicted more accurate and daily life assessment than random measurement.

Class effect of antihypertensive drug on central BP

ACEIs, ARBs, and CCBs, which are powerful vasodilators, have been known to improve central aortic pressure.[27–29] Morgan *et al.*[30] revealed that, among 4 classes of antihypertensive drugs, the lowest central aortic pressure was achieved with CCBs and diuretics. At present, published data showed that hydrochlorothiazide monotherapy is not inferior to other classes of antihypertensive drugs including CCB monotherapy in improving central BP.[12] Therefore, there is a need to compare combination therapy of CCB and hydrochlorothiazide in reducing central BP in a well-organized study design to eliminate obvious covariant. Several studies about the comparison of drug combination effects on central BP were conducted. Comparison of CCB plus ACEI and thiazide-type diuretics plus BB showed a more favorable effect in the former combination in reducing central BP than the latter combination.[10] In addition, unmatched dose of compared drug led to further mean arterial pressure reduction in CCB plus ARB arm when compared with that in the diuretics plus ARB arm.[11]

Our study was conducted to compare the 24-hour central BP-lowering efficacy of losartan combined with the most frequently prescribed CCB, fixed-dose amlodipine 5 mg, and losartan combined with the most frequently prescribed thiazide-type diuretics, hydrochlorothiazide 12.5–25 mg.[14,15] To set the office BP at the same level after the 20-week treatment on both arms, we doubled up the dose of both hydrochlorothiazide and losartan after 4 weeks of randomization, whereas losartan was doubled up with fixed-dose amlodipine 5 mg on the opponent arm when subjects had systolic office BP of ≥140 mm Hg. As a result, there were

Table 4. Factors associated with 24-hour ambulatory systolic central blood pressure (BP)

Variable	Reference	Parameter Estimate	Standard Error	*F* value	*P* value
Dependent variable: central systolic BP after 20 weeks					
***R*-square: 0.9785**					
Intercept		–13.86	3.19	18.86	<0.0001
Age	Continuous	–0.16	0.06	7.36	0.0073
20-week aPWV	Continuous	4.56	0.80	32.31	<0.0001
20-week PP	Continuous	0.58	0.03	287.94	<0.0001
20-week RM	Continuous	0.25	0.03	70.00	<0.0001
Dependent variable: differences in central systolic BP after the 20-week treatment					
***R*-square: 0.9785**					
Intercept		–13.86	3.19	18.86	<0.0001
Age	Continuous	–0.16	0.06	7.36	0.0073
20-week aPWV	Continuous	4.56	0.80	32.31	<0.0001
20-week PP	Continuous	0.58	0.03	287.94	<0.0001
20-week RM	Continuous	0.25	0.03	70.00	<0.0001

Abbreviations: aPWV, aortic pulse wave velocity; PP, pulse pressure; RM, reflection magnitude of wave.

no significant differences in office systolic/diastolic BP and mean arterial pressure after the 20-week treatment (Table 3). However, there was a significantly greater reduction in systolic central BP with amlodipine/losartan combination therapy than dose up-titrated hydrochlorothiazide/losartan therapy (Table 3; Figure 2A).

Factors associated with central systolic BP reduction

Our study results showed that 24-hour measured hemodynamic data were significantly more improved after the 20-week treatment of amlodipine compared with that of hydrochlorothiazide when combined with a balanced dose of losartan.

Numerous studies have revealed peripheral PP as a novel cardiovascular disease risk factor, although the close correlation between systolic and PP hinders efforts to distinguish these 2 hemodynamic indices.[31,32] Nowadays, direct measures of arterial stiffness and central pulsatile hemodynamic load, such as carotid–femoral PWV, central PP, and AI@75 are available.[33] Recent studies have demonstrated that carotid–femoral PWV, a direct measure of stiffness of the thoracic and abdominal aorta, is associated with higher cardiovascular disease event rates in high-risk[34,35] and community-based samples.[36–38]

The pulse wave generated from the left ventricle travels forward to peripheral arteries and partially reflected due to interactions with elastic and muscular arterial tree where changes in geometry and stiffness occur.[39] aPWV, as well as carotid–femoral PWV, is the speed with which the pulse wave travels along a length of the artery and has emerged as a classic marker of arterial stiffness and an important independent predictor of cardiovascular events.[40] There are data on the improvement of arterial stiffness with CCB[41,42] and ACEI[43–46] treatment in both animal experiments and human study. However, there are conflicting data regarding the effects of diuretics on arterial wall stiffness.[47–50] RM defined as the ratio of the amplitude of backward wave to forward wave and is strongly predictive of left ventricular remodeling and cardiovascular events.[51] The Anglo-Scandinavian Cardiovascular Outcomes Trial substudy showed that greater improvement in RM in the amlodipine/perindopril combination arm was the main factor in greater central BP reduction compared with that in the atenolol/bendroflumethiazide arm.[10] PP was determined by ventricular ejection and arterial stiffness[52,53] and arterial compliance is reversely related with PP.[54,55] Increased PP appears to be the most powerful predictive factor available to identify those patients with hypertension at greatest risk for subsequent myocardial infarction.[56] Because PP is determined by arterial stiffness and RM, drugs that affect these hemodynamic parameters might improve the PP as well.

In this study, PP, aPWV, and RM were the independent factors that associated with central systolic BP reduction in this study (Table 4). These parameters showed significantly greater reduction on amlodipine/losartan combination therapy (Table 3; Figure 2B). Improvement of PP, aPWV, and RM significantly contributed to central BP reduction after a 20-week treatment with amlodipine/losartan therapy compared with that with hydrochlorothiazide/losartan therapy.

There were no significant differences of central BP between both sexes and also the male predominance had no significant influence on central BP (Supplementary Tables 6–10).

Long-term clinical benefits of 24-hour central BP Reduction

Previous population and clinical studies have shown that 24-hour ambulatory brachial BP predicts cardiovascular

events better than office brachial BP.[57–62] At present, published data showed 24-hour ambulatory brachial BP measurements were a stronger predictor of all-cause and cardiovascular mortality than office brachial BP measurements.[63] Sporadic measurement of office central BP is known as more valuable than office brachial BP in the prediction of all-cause and cardiovascular mortalities. Also, data showed 24-hour ambulatory brachial BP measurements is more predictable for cardiovascular mortality than office central BP.[64]

However, there were no population and clinical study about long-term clinical benefits of 24-hour central BP reduction. In our study, values of 24-hour central SBP and 24-hour brachial SBP showed a strong positive correlation ($r > 0.95$, Supplementary excel data).

We showed that L/A combination is more efficacious in the reduction of 24-hour central SBP, 24-hour brachial SBP, and indices of central hemodynamics such as PWV, PP, and MR than L/H combination. The main mechanism of the reduction of 24-hour central SBP was independently associated with improvement of central hemodynamics which indices are representative of arterial compliance and stiffness.[54,55]

Legitimacy of 24-hour measurement of central BP and hemodynamics

The role of the random office central BP in risk prediction is comparable with that of 24-hour ambulatory BP.[64] Although it is still necessary to evaluate the prognostic value of 24-hour central BP, with the recent development of the ambulatory central BP system,[23,65] it may be reasonable to hypothesize that 24-hour central BP, rather than random office central BP, would be superior in terms of risk prediction.

Mobil-O-Graph BP device is feasible and reproducible method to measure 24-hour central BP and make the results reliable.[24]

Limitation of study

This was a double-blind, multicenter, randomized study with voluntary participation in the research. The characteristics of participants were male predominant and with lower-grade subclinical target organ damage shown as nearly normal PWV, AI@75, PP, and low-grade microalbuminuria. These findings are the reason for only subtle improvements in central hemodynamic parameters after the 20-week treatment even though these factors influence the central BP.

The participants were relatively young and were enrolled only after uncontrolled BP with losartan monotherapy.

CONCLUSION

The most widely prescribed CCB, amlodipine, combined with losartan therapy was more favorable on 24-hour central BP reduction compared with hydrochlorothiazide combined with losartan therapy. This central BP reduction efficacy was ascribed from reductions in aPWV, RM, and PP independent of office BP reduction.

SUPPLEMENTARY DATA

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURE

The author(s) declared no conflict of interest.

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