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ORIGINAL ARTICLE

The Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function and Atherosclerosis in Japanese Patients with Mild-to-Moderate Hypertension (J-ELAN) study

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This study was a prospective, randomized, open, blinded endpoint study to assess the effects of angiotensin II type 1 receptor blocker, losartan, compared with calcium channel blocker, amlodipine, on left ventricular (LV) diastolic function and atherosclerosis of the carotid artery in Japanese patients with mild-to-moderate hypertension, LV hypertrophy, diastolic dysfunction and preserved systolic function. Fifty-seven patients were randomly assigned to losartan- or amlodipine-based treatment groups and were followed up for 18 months. Blood pressure was similarly reduced by both regimens. Losartan shortened the transmitral E-wave deceleration time, and amlodipine reduced LV mass index; however, there was no significant difference in the percent changes of these indices between the two groups. Mean carotid intima–media thickness (mean IMT) as well as plaque score significantly increased in the amlodipine-based regimen (pre: 1.05 ± 0.26 mm, follow-up: 1.23 ± 0.33 mm, *P*=0.0015), but not in the losartan-based regimen (pre: 1.08 ± 0.35 mm, follow-up: 1.16 ± 0.52 mm, *P*=non-significant). The percent increase in mean IMT in the amlodipine-based regimen tended to be large compared with the losartan-based regimen (amlodipine: 19.8 ± 23.7%, losartan: 6.9 ± 23.3%, *P*=0.06). Under similar reduction of blood pressure, losartan is likely effective in protecting the progression of atherosclerosis of the carotid artery compared with amlodipine. Losartan may improve LV diastolic function, and amlodipine may attenuate LV hypertrophy; however, this study cannot make consecutive remarks about the superiority of either treatment regimen in the effects on cardiac function and geometry. This study has been registered at http://www.umin.ac.jp/ctr/listj/ (identifier C000000319).
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Keywords: angiotensin receptor blocker; atherosclerosis; calcium channel blocker; diastolic dysfunction

INTRODUCTION

Hypertension is one of the major risk factors of cardiovascular structural and functional impairment.[1] There have been many clinical trials to compare the effects of anti-hypertensive agents on cardiovascular function, geometry and events. However, most were conducted in the Caucasians, and the ethnic difference in the effects of pharmacological therapies is likely present,[2,3] suggesting that the results of the studies in Western countries cannot be simply extrapolated to Japanese hypertensive patients.

Left ventricular (LV) diastolic dysfunction is a risk of cardiovascular events,[4,5] and hypertension is considered as a principal cause for the progression of diastolic dysfunction in Japan, as well as Western countries.[6] Carotid atherosclerosis, another risk of cardiovascular events,[7,8] is associated with LV diastolic dysfunctions.[9] Calcium channel blocker (CCB) and angiotensin II type 1 receptor blocker (ARB) are most widely used for the treatment of hypertension in Japan, and both are expected to improve diastolic function, independent of their depressor effects. Even without the reduction of blood pressure, CCB prevents the phenotype shift of collagen synthesis;[10] ARB attenuates myocyte hypertrophy and functional alterations of calcium-handling proteins in myocyte, and prevents deposition of extracellular matrix, the phenotype shift of collagen synthesis and the cross-linked collagen accumulation.[11,12]

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This study was designed to assess the effects of the ARB, losartan, compared with the CCB, amlodipine, on LV diastolic function and atherosclerosis of the carotid artery in Japanese patients with mild-to-moderate hypertension, LV hypertrophy, diastolic dysfunction and preserved systolic function.

METHODS

The Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Japanese Patients with Mild-to-Moderate Hypertension (J-ELAN) study was a prospective, randomized, open, blinded endpoint (PROBE) design, and the rationale and complete design of this study have been published elsewhere.[13] The Ethical Committee in Osaka University Graduate School of Medicine approved this study on 27 December 2004 (No. 436), and this study was conducted in accordance with the principles stated in the Declaration of Helsinki. Written informed consent was given by all patients before entry into the study.

This study has been registered at http://www.umin.ac.jp/ctr/listj/ (identifier C000000319).

Participants and treatment

Briefly, hypertensive patients with LV hypertrophy and diastolic dysfunction who met the following entry criteria were enrolled: (1) age $\geqslant$20 years old, (2) presence of mild-to-moderate hypertension (systolic blood pressure $\geqslant$140 and $\leqslant$200 mm Hg, diastolic blood pressure $\geqslant$90 and $\leqslant$110 mm Hg), (3) presence of LV hypertrophy (the ratio of LV mass to body surface area (LV mass index) $\geqslant$120 g m^2 in men and $\geqslant$105 g m^2 in women,[14] or LV wall thickness $>$11 mm[15]), (4) presence of LV diastolic dysfunction (the ratio of peak early to late diastolic filling velocities (E/A) $<$1.0 or $>$1.5, an E-wave deceleration time (DT) $<$160 ms or $>$280 ms, isovolumic relaxation time (IRT) $<$60 ms or $>$105 ms [15]), (5) LV ejection fraction $\geqslant$50%. Patients who had been treated with angiotensin-converting enzyme (ACE) inhibitor or ARB within 5 months before enrollment, or with β-blocker or CCB within 4 weeks were excluded. Finally, 57 patients were randomized to either losartan 50 mg once daily or amlodipine 2.5 mg once daily. After 4 weeks on the initial dose, patients were titrated up to losartan 100 mg or amlodipine 5 mg once daily, depending on blood pressure response. The target blood pressure was systolic blood pressure $<$140 mm Hg and diastolic blood pressure $<$90 mm Hg. The third and fourth steps involved the addition of thiazide diuretics, α-blockers or other medication, with the exception of ARB, CCB, ACE inhibitors or β-blockers.

Data collection

In both groups, conventional transthoracic echocardiography, ultrasonography of the left and right common carotid arteries, and blood assay were conducted before and 18 months after the randomization.

Transthoracic echocardiographic examinations were conducted to measure left atrial and LV cavity sizes and LV wall thickness, as previously described.[16,17] EF was calculated by a modification of the method of Quinones *et al.*[18] and LV mass was calculated by the formula derived from the data of the American Society of Echocardiography,[19] as previously described.[16,17] The pulsed Doppler transmitral flow velocity curve was recorded to measure E/A, DT and IRT.[20] Mean carotid intima–media thickness (mean IMT) and plaque score were calculated as previously described.[21,22] These recordings and measurements were performed by sonographers from Advanced Harmonic Information Technology , Osaka, Japan, who were unaware of the study group assignment.

In addition to serum creatinine and uric acid, serum high-sensitive C-reactive protein (hs-CRP) was measured using nephelometric assay with commercially available kits (Dade Behring Marburg GmbH, Marburg, Germany). Plasma concentration of brain natriuretic peptide (BNP) was measured using chemiluminescent enzyme immunoassay with commercially available kits (Shionogi, Osaka, Japan). Plasma concentration of the amino-terminal propeptide of type III collagen was measured using immunoradiometric assay with commercially available kits (CIS Bio International, Bagnols/Ceze, France). Plasma carboxy-terminal telopeptide of collagen type I was measured using radioimmunoassay with commercially available kits (Orion Diagnostica, Espoo, Finland). These measurements were performed by FALCO Biosystems, Kyoto, Japan.

Statistical analysis

Values are expressed as mean ± s.d. All the analyses were performed according to the intention-to-treat principle using the SAS system. Baseline patient characteristics were compared using χ^2 tests and unpaired Student's t-test. Intraindividual changes following the treatment in each group were assessed using Student's t-test for paired data. Changes in parameters were presented as the ratio of the changes to the baseline values, and their difference between the groups was assessed using unpaired Student's t-test. Results were considered significant at a probability value of less than 0.05.

RESULTS

Study profile and baseline characteristics

Baseline patient characteristics are shown in Tables 1 and 2. There was no difference in age, sex ratio, blood pressure, comorbidity, echocardiographic indices, mean IMT, plaque score and data of blood test, except for left atrial dimension between the two groups. In the losartan-based treatment group (n=29), 11 patients were treated with α-blockers before the initiation of losartan, and 5 of 11 patients stopped α-blockers at the initiation. Ten patients were treated with thiazide diuretics before the initiation of losartan, and 5 of 10 patients stopped thiazide diuretics at the initiation. In the amlodipine-based treatment group (n=28), 10 patients were treated with α-blockers before the initiation of amlodipine, and 6 of 10 patients stopped α-blockers at the initiation. Twelve patients were treated with thiazide diuretics before the initiation of amlodipine, and 7 of 12 patients stopped thiazide diuretics at the initiation. There was no significant difference in the prescription ratio of additional anti-hypertensive drugs between the losartan- and amlodipine-based treatment groups.

Effects of treatment on blood pressure at follow-up for 18 months

Of 29 patients in the losartan-based treatment group, 3 were lost to follow-up: death due to infection (n=1) and withdrawal of informed consent (n=2). In the amlodipine-based treatment group, 5 of 29 patients were lost to follow-up: sudden death (n=1), withdrawal of informed consent (n=1) and other (n=3). There was no hospitalization because of cardiovascular or cerebrovascular events. Losartan was

Table 1 Baseline patient characteristics

	Losartan	*Amlodipine*	P-*value*
n	29	28	
Age (years)	61 ± 13	61 ± 9	0.911
Sex (male:female)	24:5	21:7	0.530
Systolic blood pressure (mm Hg)	150 ± 21	157 ± 18	0.188
Diastolic blood pressure (mm Hg)	91 ± 12	96 ± 14	0.151
Heart rate (b.p.m.)	76 ± 10	75 ± 13	0.923
Comorbidity (%)			
Dyslipidemia	62	57	0.790
Diabetes mellitus	10	4	0.612
Coronary artery disease	0	0	—
Cerebrovascular disease	3	4	>0.999
Medications (%)			
α-Blockers	38	36	>0.999
Diuretics	34	43	0.592
Statins	10	11	>0.999
Anti-platelet agents	10	14	0.706

Table 2 Baseline data

	Losartan	*Amlodipine*	P-*value*
Echocardiography			
LV end-diastolic dimension (mm)	46 ± 6	47 ± 7	0.420
Ejection fraction (%)	71 ± 6	73 ± 8	0.378
LV mass index (g m^2)	131 ± 33	143 ± 47	0.296
Left atrial dimension (mm)	36 ± 8	39 ± 5	0.04
E/A	0.86 ± 0.28	0.82 ± 0.21	0.452
DT (ms)	237 ± 63	236 ± 55	0.979
IRT (ms)	128 ± 61	114 ± 29	0.277
Carotid ultrasonography			
Mean IMT (mm)	1.08 ± 0.34	1.03 ± 0.27	0.572
Plaque score	5.63 ± 5.10	5.59 ± 5.30	0.980
Blood sample			
BNP (pg ml^{-1})	96 ± 169	39 ± 40	0.107
PIIIP (U ml^{-1})	0.6 ± 0.2	0.6 ± 0.3	0.760
CITP (ng ml^{-1})	4.0 ± 2.6	3.3 ± 1.1	0.212
hs-CRP (ng ml^{-1})	1004 ± 1030	2294 ± 3835	0.103
Creatinine (mg dl^{-1})	0.9 ± 0.2	0.8 ± 0.2	0.06
Uric acid (mg dl^{-1})	6.8 ± 1.7	7.1 ± 1.6	0.410

Abbreviations: BNP, brain natriuretic peptide; CITP, carboxy-terminal telopeptide of collagen type I; DT, E-wave deceleration time; *E/A*, ratio of peak early to late diastolic filling velocities; hs-CRP, high-sensitive C-reactive protein; IMT, intima–media thickness; IRT, isovolumic relaxation time; LV, left ventricular; PIIIP, aminoterminal propeptide of type III collagen.

not prescribed at follow-up in 3 of the 26 patients of the losartan-based treatment group, but the data of these patients were included in the analysis in compliance with the study design. Thus, the data of 26 patients of the losartan-based treatment group and of 23 patients of the amlodipine-based treatment group were analyzed. At 18 months after the initiation of the treatment regimens, the mean dose of losartan was 79 mg day^{-1}, and that of amlodipine was 4.8 mg day^{-1}. α-Blockers were prescribed in nine patients of the losartan-based treatment group, and thiazide diuretics were prescribed in eight patients. In the amlodipine-based treatment group, α-blockers were prescribed in 6 patients, and thiazide diuretics were prescribed in 10 patients. Anti-hypertensive medications other than α-blockers and thiazide diuretics were prescribed in one patient of the amlodipine-based treatment group and in four patients of the losartan-based treatment group. There was no significant difference in the prescription ratio of additional anti-hypertensive drugs between the losartan- and amlodipine-based treatment groups.

Systolic and diastolic blood pressures were significantly lowered in both groups. Systolic/diastolic blood pressure after an 18-month treatment was 131/80 mm Hg (s.d.: 12/10) for losartan-based regimen and 134/82 mm Hg (s.d.: 10/9) for amlodipine-based regimen. There was no significant difference between the groups. Heart rate did not change in either group.

Effects of treatment on LV geometry, LV diastolic function and atherosclerosis of the carotid artery

LV end-diastolic dimension (losartan: 45 ± 6 mm, amlodipine: 45 ± 6 mm), ejection fraction (losartan: 71 ± 8%, amlodipine: 72 ± 9%), left atrial dimension (losartan: 38 ± 7 mm, amlodipine: 38 ± 5 mm), *E/A* (losartan: 0.91 ± 0.34, amlodipine: 0.86 ± 0.25) and IRT (losartan: 117 ± 34 ms, amlodipine: 115 ± 26 ms) at follow-up were not significantly different from those before the initiation of the treatment regimen in either group. $E/A < 1$ was met at the study enrollment by 23 of 26 patients of the losartan-based regimen and 22 of the 23 patients of the amlodipine-based regimen. Even in these selected patients with low *E/A* before treatment regimen, *E/A* was not significantly changed by either treatment.

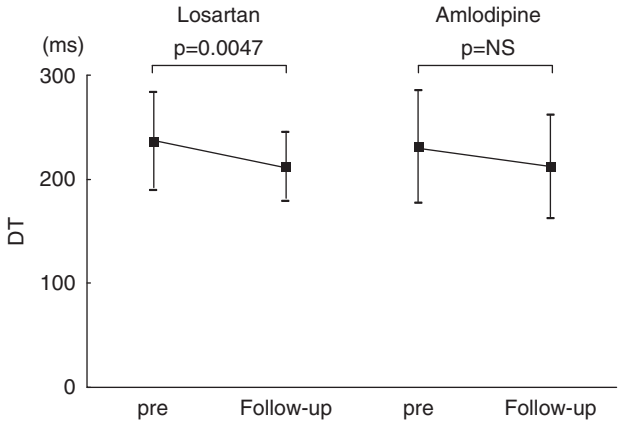

Figure 1 Changes in E-wave deceleration time (DT) in each treatment regimen.

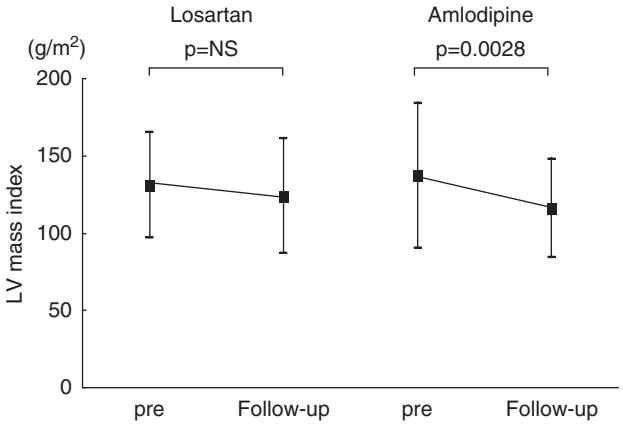

Figure 2 Changes in left ventricular (LV) mass index in each treatment regimen.

DT was significantly shortened by the losartan-based regimen (212 ± 33 ms at follow-up), but not by the amlodipine-based regimen (212 ± 50 ms at follow-up) (Figure 1). LV mass index was significantly reduced by the amlodipine-based regimen (116 ± 32 g m^2 at follow-up), but not by the losartan-based regimen (124 ± 37 g m^2 at follow-up) (Figure 2). However, the percent changes in DT or LV mass index were not significantly different between the regimens (DT: losartan −8.4 ± 13.7%, amlodipine −4.1 ± 28.3%, P=0.51; LV mass index: losartan −4.4 ± 13.7%, amlodipine −9.4 ± 24.4%, P=0.39).

The mean IMT or plaque score did not change in the losartan-based regimen (mean IMT: 1.16 ± 0.52 mm, plaque score: 7.20 ± 7.59, at follow-up), but significantly increased in the amlodipine-based regimen (mean IMT: 1.23 ± 0.33 mm, plaque score: 8.67 ± 6.38, at follow-up) (Figure 3). The percent increase in mean IMT tended to be small in the losartan-based regimen as compared with the amlodipine-based regimen (losartan: 6.9 ± 23.3%, amlodipine: 19.8 ± 23.7%, P=0.06). As there were patients whose plaque score was 0 before the initiation of the treatment regimen, the percent change in plaque score could not be compared between the groups.

BNP (losartan: 69 ± 128 pg ml^{-1}, amlodipine: 31 ± 47 pg ml^{-1}), aminoterminal propeptide of type III collagen (losartan: 0.6 ± 0.2 U ml^{-1},

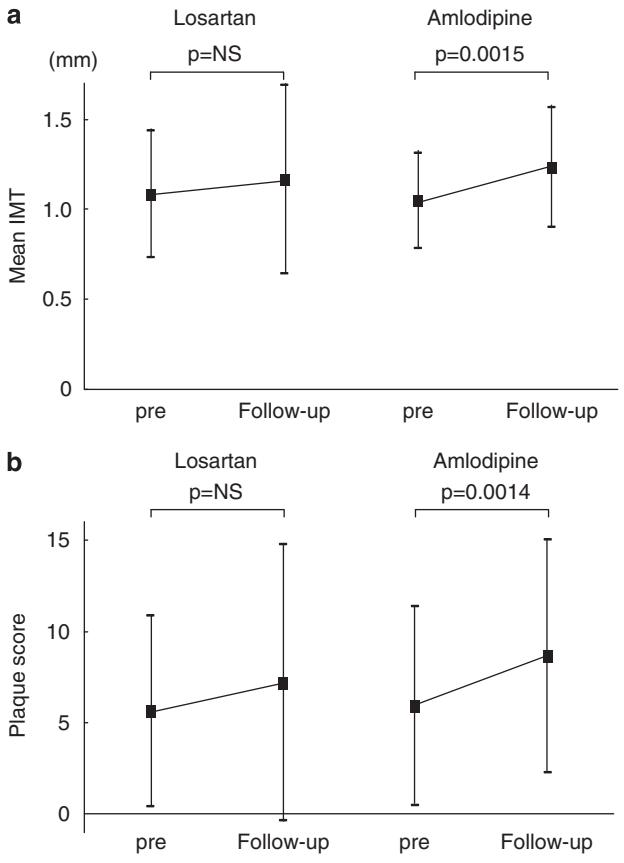

Figure 3 Changes in mean carotid intima–media thickness (mean IMT) (**a**) and plaque score (**b**) in each treatment regimen.

amlodipine: $0.6 \pm 0.1\ U\ ml^{-1}$), telopeptide of collagen type I (losartan: $3.8 \pm 2.2\ \mu g\ l^{-1}$, amlodipine: $3.2 \pm 1.0\ \mu g\ l^{-1}$), hs-CRP (losartan: $1329 \pm 2048\ mg\ dl^{-1}$, amlodipine: $4775 \pm 15583\ mg\ dl^{-1}$) and creatinine (losartan: $0.9 \pm 0.3\ mg\ dl^{-1}$, amlodipine: $0.8 \pm 0.2\ mg\ dl^{-1}$) at follow-up were not significantly different from those before the initiation of the treatment regimen in either group. Uric acid was significantly decreased by both regimens (losartan: $6.0 \pm 1.6\ mg\ dl^{-1}$, amlodipine: $6.2 \pm 1.4\ mg\ dl^{-1}$, at follow-up), and there was no difference in the percent changes between the groups (losartan: $-10.5 \pm 16.9\%$, amlodipine: $-14.3 \pm 18.2\%$).

DISCUSSION

Effects on LV diastolic function

The J-ELAN study demonstrated that the losartan-based regimen, not the amlodipine-based regimen, significantly shortened DT with the similar blood pressure reduction in patients with mild-to-moderate hypertension and diastolic dysfunction. The shortening of DT can be attributed to the improvement of diastolic function or the elevation of LV filling pressure due to the worsening of diastolic dysfunction. In the losartan-regimen group, there was no change in left atrial dimension, *E*/*A*, IRT and BNP, indicating that LV filling pressure was not increased.[23,24] These data suggest that losartan improves LV diastolic function, although there was no significant change in the other indices for diastolic function, that is, *E*/*A*, IRT and BNP. However, DT tended to decrease in the amlodipine-based regimen, and the percent decrease in DT was not different between the two treatment regimens. Thus, this study may not be allowed to make a conclusive remark about the superiority of losartan to amlodipine in the effects on LV diastolic function in Japanese hypertensive patients. The Valsartan in Diastolic Dysfunction trial demonstrated that lowering blood pressure improves diastolic function irrespective of the type of anti-hypertensive agent used.[25] Diastolic function was assessed with early diastolic mitral annular velocity recorded with tissue Doppler imaging, a sensitive non-invasive index for LV relaxation, in the Valsartan in Diastolic Dysfunction trial. If we had assessed this sensitive tissue Doppler index, we might have been able to obtain convincing results in comparing the effects of ARB and CCB on LV diastolic function.

Effects on LV geometry

The amlodipine-based regimen, not the losartan-based regimen, significantly reduced LV mass index (Figure 2). However, the percent changes in LV mass index were not different between the groups. There was no significant alteration of BNP during the follow-up period in either regimen. The current results suggest that the amlodipine-based anti-hypertensive therapy attenuates LV hypertrophy; however, the superiority of either treatment regimen to the other in the effects on LV geometry remains unclear.

The lack of changes in amino-terminal propeptide of type III collagen and carboxy-terminal telopeptide of collagen type I suggests that neither treatment regimen changed LV fibrosis. Although experimental studies have shown that ARB prevented the progression of LV fibrosis independent of its anti-hypertensive effects,[26,27] Diez *et al.*[28] showed that treatment with losartan decreased the collagen volume fraction of the ventricular wall in hypertensive patients with severe ventricular fibrosis, but not in patients without severe fibrosis. The subjects of this study had mild-to-moderate hypertension, and only one patient presented symptoms of heart failure. Thus, LV fibrosis of the study subjects may not be severe, reflecting the lack of changes in amino-terminal propeptide of type III collagen and carboxy-terminal telopeptide of collagen type I.

Effects on atherosclerosis of the carotid artery

The amlodipine-based regimen, not the losartan-based regimen, significantly increased mean IMT and plaque score (Figure 3), and the percent increase in mean IMT tended to be greater in amlodipine-based regimen than in the losartan-based regimen ($P=0.06$). It is well known that inflammation has an important role in atherosclerosis, and previous studies reported that high hs-CRP value is an independent predictor of carotid atherosclerosis progression.[29] However, hs-CRP did not significantly change in either regimen group, and there was no correlation between the changes in mean IMT and hs-CRP value in the losartan-based regimen group ($r=0.04$). Previous studies have shown that an increase in uric acid is associated with progression of atherosclerosis, because its concentration reflects oxidative stress and endothelial dysfunctions.[30] However, both treatment regimens similarly reduced serum uric acid concentration, and there was no correlation between the changes in mean IMT and uric acid in the losartan-based regimen group ($r=0.07$). Therefore, losartan may attenuate the progression of atherosclerosis through other mechanisms.

In the previous studies of the Western countries, the administration of amlodipine[31,32] or losartan[33,34] decreased IMT. In this study with Japanese patients, amlodipine significantly increased IMT and losartan did not change it, although both decreased blood pressure. The Effects of Amlodipine and Lisinopril on Left Ventricular Mass and Diastolic Function (E/A Ratio) (ELVERA) trial showed the biphasic change in IMT following the amlodipine administration, an increase in IMT at 2 years following the decrease at 1 year of the treatment.[32] However, the IMT of the amlodipine group was not decreased even at 12 months in

this study (1.16 ± 0.33 mm). The reasons for the less-protective effects of either treatment regimen on IMT in this study compared with the previous studies of the Western countries remain to be clarified. Although blood pressure was significantly reduced in this study, the ideal target blood pressure of the Japanese may be further low to induce the regression of atherosclerotic changes of carotid artery.

Nakamura *et al.*[35] recently showed that telmisartan was superior to amlodipine in protecting the worsening of IMT in Japanese hypertensive patients with moderate renal insufficiency, which is partly compatible with our results. In contrast, Ikeda *et al.*[36] reported that amlodipine, not ARBs (any of the four agents was used in 46 patients), has an inhibitory effect on early atherosclerotic process of the carotid artery in Japanese hypertensive patients with type 2 diabetes. The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial showed that candesartan- and amlodipine-based regimens produced no statistical differences in terms of the cerebrovascular events of high-risk Japanese hypertensive patients, but there was a significant difference in blood pressure between the two arms.[37] Hypertension is a major risk factor for cerebrovascular events, and further clinical studies are necessary to establish appropriate therapeutic regimens for the inhibition of atherosclerotic changes of the carotid artery in Japanese hypertensive patients.

Limitations

This study has several limitations. First, it was speculated that at least 240 patients were necessary to address the primary aim of this study, to compare the effects of ARB and CCB on LV diastolic function; however, only 57 patients were enrolled. Second, the observational period of this study was only 18 months with the small number of study subjects and the assessment of the effects on surrogate markers. Pharmacological anti-hypertensive interventions within 1 year clarified the significant difference in effects on surrogate markers observed in previous clinical studies.[38–40] If the number of study subjects was much more in this study, we might have observed a clear difference in the effects on markers between the two regimens. However, the desirable endpoints of clinical trials are cardiovascular and cerebrovascular events and death, and hence future clinical studies with more patients and longer observational period are required. Third, electrocardiographic changes were not assessed in this study, and the comparison with previous studies was not allowed in this standpoint.

CONCLUSIONS

Under the similar reduction of blood pressure, losartan is likely effective in protecting the progression of atherosclerosis of the carotid artery compared with amlodipine in Japanese patients with mild-to-moderate hypertension, LV hypertrophy, diastolic dysfunction and preserved systolic function, and its benefits may be provided through mechanisms other than anti-inflammatory effects. Losartan may improve LV diastolic function, and amlodipine may attenuate LV hypertrophy; however, this study cannot make consecutive remarks about the superiority of either treatment regimen in the effects on cardiac function and geometry.

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