Arterial-Cardiac Destiffening Following Long-Term Antihypertensive Treatment

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BACKGROUND
We examined whether in addition to producing a greater degree of improvement of the arterial stiffness, long-term angiotensin II receptor blocker (ARB) treatment might also have a more beneficial effect on the cardiac diastolic dysfunction than long-term calcium-channel blocker (CCB) treatment; we also evaluated the association between the improvements of the two variables brought about by ARB treatment in subjects with stage I or II hypertension.

METHODS
One hundred and thirteen patients were randomly allocated to treatment with an ARB (candesartan) or a CCB (amlodipine). Echocardiography and measurement of the brachial-ankle pulse wave velocity (PWV) were conducted in both groups at the start of the treatment and at the end of 2–3-years’ treatment.

RESULTS
After adjustments for covariates, the extent of reduction of the brachial-ankle PWV (−200 ± 18 cm/s vs. −141 ± 18 cm/s, P = 0.03) and that of the increase of the E/A ratio (0.08 ± 0.03 vs. 0.01 ± 0.03, P = 0.04) were significantly greater in the candesartan group than in the amlodipine group. A significant relationship was identified between the delta changes of the brachial-ankle PWV and delta changes of the E/A ratio observed following long-term candesartan treatment.

CONCLUSION
Long-term candesartan treatment may have a more beneficial effect on the stiffness of the large- to- middle-sized arteries than long-term amlodipine treatment, and this treatment may also concomitantly improve the cardiac diastolic dysfunction; a significant association appeared to exist between the improvements of the two variables observed following long-term candesartan treatment.

Keywords: arterial stiffness; blood pressure; cardiac diastolic function; hypertension; renin–angiotensin system

A recent meta-analysis confirmed that increased arterial stiffness, as reflected by an increased pulse wave velocity (PWV), is an independent predictor of future cardiovascular events,¹ as it exerts unfavorable effects on the cardiovascular system.²,³ Experimental studies have demonstrated that the renin-angiotensin (RA) system plays pivotal roles in the progression of arterial stiffening, and that blockade of this system alleviates such progression.⁴ While several clinical studies have demonstrated the beneficial effects of angiotensin II receptor blockers (ARBs) on arterial destiffening,⁵,⁶ only treatment outcomes over the short-term were evaluated in most of these studies (i.e., 3–6 months’ treatment). Aging is a major factor promoting the progression of arterial stiffening,⁷ and our previous preliminary study failed to confirm a favorable effect of short-term ARB treatment (8-months’ treatment) on arterial destiffening.⁸ However, it has not yet been clarified whether long-term ARB treatment might have a favorable effect on arterial destiffening by counteracting the progression of arterial stiffening caused by aging.

Increased arterial stiffness has been reported to be associated with cardiac diastolic dysfunction in patients with hypertension.⁹ Heart failure with preserved ejection fraction (diastolic heart failure) is considered as one of the cardiac complications of increased arterial stiffness in subjects with hypertension.¹⁰–¹⁴ The effects of ARBs on the cardiac diastolic function are still controversial.¹⁵,¹⁶ Furthermore, the possible existence of a correlation between the beneficial effects of ARBs on arterial destiffening and ARB-induced improvement of the cardiac diastolic dysfunction has not yet been precisely clarified.

Therefore, we conducted the present prospective study, using a study design modified from our previous study, in subjects with stage I or II hypertension to examine the following: (i) whether long-term ARB treatment might have a more beneficial effect on the progression of arterial stiffening than long-term calcium-channel blocker (CCB) treatment; (ii) whether this treatment might also concomitantly improve cardiac diastolic function; (iii) whether the association between the improvements of the arterial stiffness and cardiac diastolic dysfunction might only be observed in patients treated with ARBs, and not in those treated with CCBs.

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**METHODS**

*Principle of modification of the original study design.* The present study design was modified from our previous study design, which has been reported in detail elsewhere. Briefly, in our previous study, we evaluated the association between the changes in the insulin sensitivity and improvement of the endothelial function following treatment with candesartan (a popularly prescribed ARB in Japan) and amlodipine (a popularly prescribed CCB in Japan). The participants of the present study received candesartan or amlodipine, in addition to other classes of antihypertensive medications, e.g., diuretics and/or β-blockers, at 30 min after breakfast; subjects that did not have breakfast took the drugs in the morning. The modified design of the present study, conducted in two parts, was as follows: (i) the follow-up period of the original study subjects was extended, and blood chemistry examinations, echocardiography and measurement of the brachial-ankle PWV were conducted again after 2–3 years of antihypertensive drug treatment; (ii) a *de novo* protocol was introduced to increase the number of study subjects, and the enrollment period for this *de novo* protocol was 24–28 months. Written informed consent was obtained from all of the subjects before their participation in the study. The protocol of the study was approved by the ethics committee of Tokyo Medical University.

**The study subjects.** Among consecutive patients with hypertension who visited the outpatient clinic of the Tokyo Medical University Hospital between November 2002 and December 2005 or between January 2006 and June 2009, the subjects fulfilling the following criteria were enrolled in the original and modified studies: among three visits to the clinic at 4–6-week intervals, systolic blood pressure <180 mm Hg (average, 140–180 mm Hg) and/or diastolic blood pressure <110 mm Hg (average, 90–110 mm Hg); no symptoms suggestive of cardiovascular disease; no electrocardiographic abnormalities except left-ventricular hypertrophy (i.e., high-voltage QRS complexes and/or ST/T changes characteristic associated with left-ventricular hypertrophy). Therapeutic lifestyle modifications were recommended in accordance with the recommendations of the Japanese Society of Hypertension 2000 and the Japanese Society of Hypertension 2004 guideline.

Subjects with the following conditions were excluded from the study: fasting plasma glucose >125 mg/dl; serum creatinine concentration ≥2.0 mg/dl; previous history of medication for hypertension, and/or other atherosclerotic cardiovascular diseases; serious underlying medical problems, e.g., diabetes and/or dyslipidemia, requiring specific medical treatments such as oral hypoglycemic agents, insulin, statins, and/or fibrates; ankle-brachial pressure index <0.95; left-ventricular ejection fraction as assessed by echocardiography <50%.

**Study design**

*The original study protocol and the extended study.* The original study was conducted as a prospective open-labeled study between November 2002 and December 2005. The study design is described in detail elsewhere. The patients who were entered into the study protocol were randomly allocated to treatment with either an ARB (candesartan, 8 mg/day) or a CCB (amlodipine, 5 mg/day), with the target blood pressure set to below 140/90 mm Hg by the end of the 2nd month of treatment. During this period, trichlormethiazide at 1 mg/day as a 2nd agent, and bisoprolol at 5 mg/day as a 3rd agent were added as necessary. Blood chemistry examinations, echocardiography, and measurement of the brachial-ankle PWV were conducted at the start and at the end of 8-months’ treatment.

Seventy-one patients were successfully entered into the original analysis conducted after 8-months’ treatment, and thereafter, these patients were followed up routinely at the outpatient department of Tokyo Medical University Hospital (they visited the outpatient department every 2 months). Then, among these subjects, those who satisfied following criteria were selected for the present analysis: (i) 3rd examinations (blood chemistry examinations, echocardiography, and measurement of the brachial-ankle PWV) were conducted after 2–3-years’ treatment; (ii) continuation of candesartan-based treatment without prescribing CCBs, or of amlodipine-based treatment, without prescribing ARBs until the 3rd examinations. During this extended study period, the maximum dose used of candesartan was 12 mg/day and that of amlodipine was 10 mg/day (both representing the maximum dosages used in Japan).

*De novo study design:* The study subjects were similar to those in the original study, and this *de novo* study was conducted between January 2006 and June 2009. Until the end of the 2nd month of treatment, the study protocol was similar to that in the original study. In the *de novo* protocol, if the target blood pressure of <140/90 mm Hg was not achieved by the end of 2-months’ treatment (step 1 medication), titration of the dose (i.e., of candesartan up to 12 mg/day and amlodipine up to 10 mg/day) was conducted until the end of the 3rd month (step 2 medication). Then, the patients were followed-up at the outpatient department every 2 months. Blood chemistry examinations, echocardiography, and measurement of the brachial-ankle PWV were conducted at the start of the treatment, at the end of 8-months’ treatment, and at the end of 24–28-months’ treatment.

In both study protocols, after the 8th month, a statin was prescribed for patients in whom the lifestyle modifications failed to reduce the serum levels of low-density lipoprotein cholesterol to below 140 mg/dl.

**Measurements.** In the present study, brachial-ankle PWV was used as a marker of arterial stiffness, and the peak velocity of early rapid filling (E velocity)/peak velocity of atrial filling (A velocity) ratio (E/A ratio) obtained by ultrasound examination of the heart was used as a marker of cardiac diastolic function. The procedural details of these measurements are described below.

**Blood pressure measurement:** Until the end of December 2005, systolic and diastolic blood pressures were determined based on Korotkoff sounds, and from the January 2006, the blood pressure measurement was based on the oscillometric method (Omron HEM-907; OMRON Health Care, Kyoto, Japan).
Ultrasonographic examination of the heart: M-mode echocardiograms were obtained by two-dimensional echocardiography using an echocardiography instrument equipped with a 3.0–5.0-MHz transducer. The mean of two M-mode measurements obtained by two investigators was used. The left-ventricular mass index was calculated by Devereux’s method. The left-ventricular mass index was estimated as the left-ventricular mass divided by the body surface area. Relative wall thickness at diastole was calculated by the formula, relative wall thickness at diastole = (2 × thickness of left-ventricular posterior wall/left-ventricular diameter at diastole). The left-ventricular systolic and diastolic volumes and ejection fraction were derived from the M-mode images according to standard criteria. Pulsed Doppler measurements of the left-ventricular diastolic inflow were obtained under two-dimensional echocardiographic guidance. Briefly, the left-ventricular diastolic filling pattern was recorded from the apical transducer position in patients in the partial left lateral decubitus position during expiratory apnea, the sampling volume situated between the mitral leaflet tips. The E velocity and A velocity were recorded, and the E/A ratio and deceleration time were calculated as the interval from the E-wave peak to decline of the velocity to the baseline values obtained from three consecutive cardiac cycles.

PWV: Brachial-ankle PWV was measured using a volume-plethymographic apparatus (Form/ABI; OMRON Colin, Kyoto, Japan). Details of the methodology are described elsewhere. The measurements were conducted with the subjects resting in the supine position. Electroderecographic electrodes were placed on both wrists, and cuffs were wrapped on both the arms and ankles. The pulse volume waveform at the brachium and ankle were recorded using a semiconductor pressure sensor after the patient had rested for at least 5 min. Validation of this method has been reported elsewhere.

Laboratory measurements: Serum levels of high-density lipoprotein cholesterol, low-density lipoprotein, triglycerides, and serum creatinine, and the fasting plasma glucose were measured enzymatically in fasting blood samples obtained from the subjects. Plasma B-type natriuretic peptide (BNP) (Shionoria BNP kit; Shionogi, Osaka, Japan) levels were determined by radioimmunoassay. Blood samples were obtained in the morning. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation modified for the Japanese population (i.e., 194 × (serum creatinine concentration)^-1.094 × (age)^0.287 × (0.739 for women)).

Statistics. All the data were expressed as mean ± s.d. The differences in the values of the variables between the start, end of 8-months’ treatment, and end of 2–3-years’ treatment were calculated as the delta changes: values at the end of 8-months’ treatment or end of 2–3-years’ treatment minus those at the start of the treatment. The relationships between the variables were assessed by simple linear regression analysis and multiple linear regression analysis. The significances of the differences in the values measured before and after the treatments were evaluated using a paired t-test. The difference in each variable between the two study groups (candesartan vs. amlodipine) was evaluated using an unpaired t-test for continuous variables. In addition, a general linear model multivariate analysis post hoc pairwise comparisons model with adjustments was used to compare the delta changes of the brachial-ankle PWV and that of the E/A ratio in the short-term and over the long-term between the candesartan and amlodipine treatment groups. The covariates adjusted for included the patient’s age, gender, smoking status and change of smoking status, changes of the mean blood pressure, heart rate, high-density lipoprotein, low-density lipoprotein, triglycerides and Crnn, changes of fasting plasma glucose, treatment with diuretics, β-blockers and/or statins, and the duration of follow-up. A general linear model with interaction terms was applied to assess the significance of the difference in the relationship of the delta changes of the brachial-ankle PWV to those of the E/A ratio between the two treatment groups; a P value of <0.05 was considered as indicative of statistically significant difference. All the analyses were conducted using the IBM/SPSS (17.0) for Windows; IBM/SPSS, Chicago, IL).

RESULTS

Among the 71 original study patients, one patient did not agree for re-entry into the study protocol, one patient failed to return for the follow-ups, two patients failed undergo echocardiography at the end of 2–3 years’ treatment, and five patients were prescribed a change of the medications. Finally, 62 of the original study subjects were selected for the extended study. In the de novo study, of the 53 patients who had been entered into this de novo protocol initially, one patient was lost to follow-up and one patient was withdrawn from the study because of the development of hot flashes caused by amlodipine. Finally, the data of a total of 113 patients (i.e., 62 extended original study subjects and 51 de novo study patients) were included for the final analysis. The mean duration of follow-up was similar between the two groups (30 ± 5 months in extended original study group and 29 ± 5 months in de novo study group). In addition, the delta changes of the brachial-ankle PWV and E/A ratio during the study period were also similar between the two groups (data not shown).

Table 1 shows the clinical characteristics of the study subjects and the changes in the measured variables in the candesartan and amlodipine groups. The blood pressure decreased significantly to similar extents in both the treatment groups. No significant changes in the fasting plasma glucose or serum lipid profile were observed in either group, but four patients in the candesartan group and four in the amlodipine group required initiation of a statin after 8-months’ antihypertensive treatment. A significant decrease of the brachial-ankle PWV was observed in the short-term as well as over the long-term, in both the long-term candesartan and amlodipine treatment groups. Significant increase of the E/A ratio and significant decrease of the plasma levels of BNP were observed after long-term candesartan, but not long-term amlodipine treatment. On the other hand, significant reduction, to similar extents, of the left-ventricular mass index and relative wall thickness at diastole was observed in both the treatment groups (Table 2).
The crude values of the delta change of the brachial-ankle PWV were similar not only between the short-term ARB and CCB treatment groups (ARB: \(-155 \pm 197 \text{ cm/s}\) vs. CCB: \(-151 \pm 200 \text{ cm/s}\) \((P = 0.93)\)), but also between the long-term ARB and CCB treatment groups (ARB: \(-180 \pm 203 \text{ cm/s}\) vs. CCB: \(-162 \pm 207 \text{ cm/s}\) \((P = 0.53)\)). On the other hand, while the crude values of the delta change of the E/A ratio were similar between the two short-term treatment groups (ARB: \(0.06 \pm 0.21\) vs. CCB: \(0.01 \pm 0.32\) \((P = 0.36)\), this value was greater in the long-term ARB treatment \((0.08 \pm 0.16)\) than that in the long-term CCB treatment group \((0.01 \pm 0.22)\) \((P = 0.04)\).

Figure 1 depicts the adjusted values of the delta changes of the brachial-ankle PWV and those of the E/A ratio following both short-term and long-term treatment with both drug classes. (The covariates for the adjustments are described in detail in the Statistics section). In the short-term, the adjusted values of

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**Table 1 | Clinical characteristics of the patients and the changes in the values of the variables following candesartan- and amlodipine treatment**

<table>
<thead>
<tr>
<th></th>
<th>Candesartan-based treatment ((n = 56))</th>
<th>Amlodipine-based treatment ((n = 57))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56 ± 10</td>
<td>58 ± 11</td>
</tr>
<tr>
<td>Duration</td>
<td>30 ± 5</td>
<td>29 ± 5</td>
</tr>
<tr>
<td>Male/female</td>
<td>36/20</td>
<td>36/21</td>
</tr>
<tr>
<td>Smoking</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>BMI</td>
<td>24.1 ± 3.6</td>
<td>24.1 ± 3.6</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>153 ± 18</td>
<td>129 ± 12</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>88 ± 12</td>
<td>78 ± 9</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>125 ± 24</td>
<td>118 ± 30</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>57 ± 14</td>
<td>56 ± 15</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>130 ± 88</td>
<td>128 ± 86</td>
</tr>
<tr>
<td>CRN (mg/dl)</td>
<td>106 ± 14</td>
<td>106 ± 14</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>67 ± 18</td>
<td>69 ± 17</td>
</tr>
<tr>
<td>baPWV (cm/s)</td>
<td>1,741 ± 356</td>
<td>1,576 ± 263</td>
</tr>
</tbody>
</table>

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**Table 2 | Echocardiographic parameters and plasma B-type natriuretic peptide levels and the changes in the values of these variables following candesartan- and amlodipine treatment**

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>8th month</th>
<th>pI8m</th>
<th>2nd year</th>
<th>pI2y</th>
<th>p8m2y</th>
<th>Initial</th>
<th>8th month</th>
<th>pI8m</th>
<th>2nd year</th>
<th>pI2y</th>
<th>p8m2y</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI (g/m²)</td>
<td>126 ± 21</td>
<td>119 ± 23</td>
<td>0.02</td>
<td>119 ± 21</td>
<td>0.03</td>
<td>0.67</td>
<td>123 ± 24</td>
<td>118 ± 25</td>
<td>0.04</td>
<td>117 ± 25</td>
<td>0.03</td>
<td>0.74</td>
</tr>
<tr>
<td>RWTd</td>
<td>0.45 ± 0.05</td>
<td>0.44 ± 0.04</td>
<td>&lt;0.01</td>
<td>0.43 ± 0.04</td>
<td>&lt;0.01</td>
<td>0.35</td>
<td>0.45 ± 0.05</td>
<td>0.44 ± 0.05</td>
<td>0.03</td>
<td>0.43 ± 0.05</td>
<td>0.02</td>
<td>0.39</td>
</tr>
<tr>
<td>EF (%)</td>
<td>66 ± 6</td>
<td>66 ± 5</td>
<td>0.86</td>
<td>67 ± 4</td>
<td>0.42</td>
<td>0.40</td>
<td>67 ± 6</td>
<td>68 ± 5</td>
<td>0.07</td>
<td>68 ± 4</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>FS (%)</td>
<td>36 ± 4</td>
<td>37 ± 3</td>
<td>0.74</td>
<td>37 ± 3</td>
<td>0.72</td>
<td>0.96</td>
<td>37 ± 4</td>
<td>38 ± 4</td>
<td>0.18</td>
<td>38 ± 4</td>
<td>0.20</td>
<td>0.99</td>
</tr>
<tr>
<td>DCT</td>
<td>200 ± 35</td>
<td>196 ± 24</td>
<td>0.18</td>
<td>202 ± 35</td>
<td>0.61</td>
<td>0.08</td>
<td>194 ± 39</td>
<td>194 ± 32</td>
<td>0.52</td>
<td>189 ± 32</td>
<td>0.24</td>
<td>0.75</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.85 ± 0.24</td>
<td>0.90 ± 0.24</td>
<td>0.04</td>
<td>0.94 ± 0.23</td>
<td>&lt;0.01</td>
<td>0.47</td>
<td>0.93 ± 0.39</td>
<td>0.94 ± 0.28</td>
<td>0.73</td>
<td>0.94 ± 0.27</td>
<td>0.67</td>
<td>0.96</td>
</tr>
<tr>
<td>BNP (pg/dl)</td>
<td>19.6 ± 26.7</td>
<td>14.2 ± 11.6</td>
<td>0.06</td>
<td>13.1 ± 12.0</td>
<td>0.04</td>
<td>0.56</td>
<td>19.4 ± 16.1</td>
<td>20.0 ± 26.7</td>
<td>0.82</td>
<td>19.0 ± 16.2</td>
<td>0.86</td>
<td>0.71</td>
</tr>
</tbody>
</table>
the delta changes of the brachial-ankle PWV and that of E/A ratio were similar between the two treatment groups. In contrast, the extent of reduction of the brachial-ankle PWV and that of the increase of the E/A ratio were significantly greater in the long-term candesartan treatment group than in the long-term amlodipine treatment group.

A general linear model analysis demonstrated that the effects of the two drug classes (candesartan and amlodipine) and the delta changes of the brachial-ankle PWV showed a significant interaction with those of the E/A ratio (nonstandardized coefficient (95% confidence interval) = −0.01 (−0.01–0.00); Wald test = 5.45, \( P = 0.02 \)). As shown in Figure 2, a significant relationship was observed between the delta changes of the brachial-ankle PWV and those of the E/A ratio following long-term treatment with candesartan, but not in the long-term amlodipine treatment group. Multiple linear regression analysis with adjustments for covariates (the covariates are described in detail in the Statistics section) demonstrated a significant relationship between the delta changes of the brachial-ankle PWV (nonstandardized coefficient = 47.68 (95% confidential intervals = 1.08–98.71), standardized coefficient = 0.12, \( P = 0.03 \)) and those of the E/A ratio (nonstandardized coefficient = −0.08 (95% confidential intervals = −0.18 to −0.01), standardized coefficient = −0.17, \( P = 0.02 \)) following long-term candesartan treatment.

Among the study patients, the blood pressure was successfully controlled to below 140/90 mm Hg by candesartan alone in 30 patients and by amlodipine alone in 38 patients. The adjusted values of the delta changes of the brachial-ankle PWV following long-term treatment was larger in the candesartan group (186 ± 24 cm/s) than in the amlodipine group (117 ± 20 cm/s) (\( P = 0.02 \)).

**DISCUSSION**

To the best of our knowledge, the present study is the first to evaluate the favorable effects of long-term ARB treatment on arterial destiffening and the concomitant improvement of the cardiac diastolic dysfunction in patients with stage I or II hypertension. In addition, the significance of the relationship between the improvements in the two parameters was also evaluated.

The patient follow-up duration in previous studies investigating the favorable effects of ARBs on the arterial stiffness has, in general, not been more than a few months. Recently, Ait-Oufella et al. reported a sustained decrease of the aortic stiffness following long-term antihypertensive treatment (mean duration of follow-up, 5.3 years). Blood pressure is a major determinant of the PWV, producing functional stiffening of the arteries. Thus, one of the important findings of the present study was that the pressure-independent reduction of the brachial-ankle PWV was greater after long-term (2.5 years) candesartan treatment than after long-term (2.5 years) amlodipine treatment (i.e., candesartan might produce structural destiffening of the arteries), although no such difference between the two drug groups was noted following short-term treatment (8 months). Increased arterial stiffness, especially of the large arteries, increases the cardiovascular
risk via several mechanisms. On the other hand, the brachial-ankle PWV reflects the stiffness of the large- to middle-sized arteries and it could not be concluded from the results of the present study whether long-term candesartan treatment mainly improved the stiffness of large arteries, a key element related to cardiovascular risk, or that of the middle-sized arteries, or both.

Either way, the reduction of the arterial stiffness improved the cardiac afterload, because significant reduction of the plasma levels of BNP was observed following candesartan treatment. BNP is an independent predictor of a high left-ventricular end-diastolic pressure, and plasma BNP levels are known to be elevated in patients with cardiac diastolic dysfunction. Elevated plasma natriuretic peptide levels are reported as an independent risk factor for cardiovascular events, and reduction of the brachial-ankle PWV by antihypertensive treatment might be favorable for reduction of the cardiovascular risk. The CASE-J study reported no significant difference in terms of the cardiovascular endpoint between candesartan and amlodipine treatment groups, however, the study period was only 3.2 years.

Thus, considering the results of the present study, a further study with a longer duration of follow-up is proposed to compare the effects of ARB and CCB treatment on the incidence of cardiovascular events, especially heart failure.

Both CCBs and ARBs have been reported to improve the cardiac diastolic function in subjects with hypertension, and the VALIDD study reported that the degree of improvement of the cardiac diastolic dysfunction following 38 weeks of ARB treatment was not significantly different from that following 38 weeks of treatment with other antihypertensive agents. However, the present long-term study (>2 years) confirmed a greater beneficial effect of candesartan, as compared to that of amlodipine, on both the arterial stiffness and the cardiac diastolic function. A significant relationship between the changes in the two parameters was observed following long-term treatment in the candesartan group, but not in the amlodipine group, in this study. Therefore, it might be speculated that the RA system may modulate this association.

Left-ventricular hypertrophy and cardiac fibrosis contribute to cardiac diastolic dysfunction. While a recent meta-analysis reported that greater regression of left-ventricular hypertrophy was observed following treatment with an ARB than that following treatment with other antihypertensive agents, in the present study, the two agents produced a similar degree of regression of the left-ventricular mass index. We propose two plausible mechanisms underlying the significant relationship between the changes of the arterial stiffness and the changes of the cardiac diastolic function in patients on long-term treatment with candesartan. (i) The RA system contributes to vascular and cardiac fibrosis, and the reduction of the fibrosis associated with RA blockade by an ARB might contribute not only to improvement of the arterial stiffness, but also, at least in part, to that of the cardiac diastolic function. (ii) Arterial stiffness causes myocardial fibrosis by causing a direct increase of the cardiac afterload and/or by inducing subendocardial ischemia through impaired coronary perfusion.

The present study had the following limitations: (i) It was an open-label and varying-protocol study. (ii) Although the brachial-ankle PWV can be easily and repeatedly measured in a large number of study subjects and is known to show a close correlation with the carotid-femoral PWV, the gold standard for assessment of the aortic stiffness is measurement of the carotid-femoral PWV. Therefore, a study to confirm that long-term ARB treatment produces a greater degree of improvement of the large-arterial stiffness than long-term CCB treatment is proposed in the future. (iii) Arterial-ventricular coupling is a key to the association between the arterial stiffness and the cardiac systolic and diastolic functions, however, the systolic and diastolic cardiac stiffnesses were not measured in this study. (iv) Physical activity affects the arterial stiffness, however, we did not assess the levels of physical activity of the subjects in this study. (v) One possible reason for the absence of a significant effect of amlodipine on the cardiac diastolic function was that the left-ventricular hypertrophy, a key factor affecting diastolic function, was mild in all of the present study subjects, therefore, the extent of regression of left-ventricular hypertrophy in the amlodipine group may not have been sufficient to produce a significant effect on the cardiac diastolic function. (vi) No data were available to estimate the sample size for evaluating the differences in the effects between two antihypertensive drugs on reduction of brachial-ankle PWV. (vii) The 24-h blood pressure levels, especially nighttime blood pressure levels, is a strong predictor of future cardiovascular events. This means that diurnal blood pressure variations and their pattern might be related to the risk/intensity cardiovascular damage, however, the difference in the effect between candesartan and amlodipine on the diurnal blood pressure variations was not evaluated in this study.

Long-term candesartan treatment may produce greater improvement of the stiffness of the large- to middle-sized arteries than long-term amlodipine treatment, and this favorable effect on the arterial stiffness may also contribute to the concomitant improvement of the cardiac diastolic dysfunction in patients treated with candesartan. Furthermore, a significant association was identified between the improvements of the two parameters following long-term candesartan treatment, which could not be recognized following long-term amlodipine treatment. Thus, it would appear that long-term RA blockade is favorable for arterial-cardiac destiffening.

Disclosure: The authors declared no conflict of interest.


