Effects of Amlodipine and Candesartan on Arterial Stiffness Estimated by Cardio-Ankle Vascular Index in Patients with Essential Hypertension: A 24-Week Study

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ABSTRACT

BACKGROUND: Aortic stiffness assessed by brachio-ankle pulse wave velocity (baPWV) can be used to predict cardiovascular events. However, baPWV is dependent on blood pressure. Antihypertensive drugs have been reported to reduce baPWV; but it is difficult to determine if this effect is associated with lowered blood pressure or reduced arterial stiffness.

OBJECTIVES: The primary end point of this study was to assess whether antihypertensive drugs reduce arterial stiffness as estimated by cardio-ankle vascular index (CAVI). The secondary end point was to compare the effects of 2 widely used drugs, the calcium-channel blocker amlodipine and the angiotensin II receptor blocker candesartan, on arterial stiffness.

METHODS: Between October 2005 and September 2006, consecutive Japanese outpatients with essential hypertension (EHT) (defined as using antihypertensive drugs at screening, systolic blood pressure [SBP] >140 mm Hg, or diastolic BP [DBP] >90 mm Hg) were assigned to treatment for 24 weeks with either amlodipine (5–10 mg/d) or candesartan (8–12 mg/d). Arterial stiffness was evaluated with CAVI before and after 24 weeks of treatment. Relative change in arterial stiffness from baseline was also compared. The evaluator was blinded to treatment.

RESULTS: Twenty patients (11 men, 9 women; mean [SD] age, 62 [10] years) were included in the study. There were no significant differences in clinical characteristics between the 2 groups. At baseline, mean (SD) CAVI was not significantly different in the amlodipine group compared with the candesartan group (8.93 [0.93] vs 8.46 [1.34], respectively). During the 24-week treatment period, mean SBP and DBP decreased significantly in both the amlodipine (14/10 mm Hg; \( P = 0.006 \) and \( P = 0.005 \)) and the candesartan groups (13/11 mm Hg; \( P = 0.033 \) and \( P = 0.005 \)). Amlodipine was associated with a significant change in CAVI from baseline (8.93 [0.93] vs 8.60 [1.50]; \( P = 0.017 \)), whereas candesartan was not (8.46 [1.34] vs 8.81 [1.20]). The percentage change in CAVI was significantly different in the amlodipine group compared with the candesartan group (−7.14 [8.83] vs 5.85 [16.0], respec-
tively; \( P = 0.038 \). After 24 weeks of treatment, the CAVI of the amlodipine group was still numerically larger than baseline CAVI of the candesartan group, although the difference was not statistically significant. Furthermore, there was no significant difference in absolute CAVI between the 2 groups after 24 weeks, but the relative change from baseline was significant in favor of amlodipine. Logistic regression analysis revealed that amlodipine improved CAVI independent of its antihypertensive effect.

**CONCLUSION:** These data suggest that amlodipine and candesartan had different effects on aortic stiffness estimated by CAVI, despite similar effects on brachial blood pressure after 24 weeks of treatment in these Japanese patients with EHT. (Curr Ther Res Clin Exp. 2008;69:412–422) © 2008 Excerpta Medica Inc.

**KEY WORDS:** arterial stiffness, amlodipine, candesartan, cardio-ankle vascular index.

**INTRODUCTION**
Arterial stiffness increases with age and is associated with pathological conditions, including hypertension, diabetes mellitus, and end-stage renal disease.\(^1\)\(^2\) It is also considered a marker for cardiovascular risk factors and organ damage.\(^3\)\(^5\)

Carotid-femoral pulse wave velocity (cfPWV) is used to evaluate arterial stiffness, but a femoral artery transducer adjusted to obtain an accurate pulse wave is required. Brachio-ankle PWV (baPWV) is a more convenient index for evaluating arterial stiffness. However, a problem with the clinical use of baPWV is its strong dependence on blood pressure during measurement.\(^6\) To overcome this disadvantage, a stiffness diagnostic parameter called the cardio-ankle vascular index (CAVI) was developed in Japan.\(^7\)\(^8\) Hayashi et al\(^9\) proposed the stiffness parameter \( \beta \), which represents the local stiffness of a blood vessel. The parameter is based on a change in vascular diameter (\( \Delta D \)) corresponding to arterial pressure. Kawasaki et al\(^10\) defined \( \beta \) as follows:

\[
\ln \left( \frac{P_s}{P_d} \right) \times \frac{D}{\Delta D},
\]

where \( \ln \) is the natural log, \( P_s \) is systolic arterial pressure, and \( P_d \) is diastolic arterial pressure. The formula enabled the measurement of \( \beta \) with an echo-phase tracking system. Using this algorithm, the CAVI formula was created.\(^8\)

We reported previously that CAVI was closely correlated with other stiffness parameters, such as the stiffness \( \beta \) and cross-sectional distensibility coefficients estimated by carotid ultrasonography in patients with essential hypertension (EHT).\(^11\) An association has also been found between CAVI and carotid intima-media thickness\(^5\) and left ventricular diastolic function.\(^12\) These results indicate that, similar to baPWV, CAVI might be a useful clinical marker for evaluating atherosclerosis and arteriosclerosis.\(^6\)

Angiotensin II receptor blockers (ARBs) were reported to reduce arterial stiffness estimated by baPWV in hypertensive patients.\(^13\) However, because measurement of baPWV is highly dependent on blood pressure, it is difficult to know whether the improvement in arterial stiffness associated with antihypertensive drugs is mediated by their blood pressure-lowering effects or is a result of the direct effects on blood vessels.
Calcium channel blockers (CCBs) are commonly used antihypertensive drugs in Japan. Long-acting CCBs reduce the incidence of major cardiovascular events, especially stroke. Amlodipine was found to reduce adverse cardiovascular events in normotensive patients with coronary artery disease, whereas the angiotensin-converting enzyme inhibitor enalapril had no such effect. Amlodipine may have a cardiovascular protective effect in addition to its strong blood pressure–lowering action. It has been reported to have several blood pressure–independent effects, including antioxidant activity, antiproliferative effects in vascular smooth muscle cells, and enhanced production of endothelial nitric oxide.

The primary end point in this study was to assess whether antihypertensive drugs reduce arterial stiffness estimated by CAVI in Japanese patients with EHT. The secondary end point was to compare the effects on arterial stiffness of 2 widely used drugs, the CCB amlodipine and the ARB candesartan.

PATIENTS AND METHODS

Study Patients

The ethics committee of Ehime University Hospital, Ehime, Japan, approved the study, and written informed consent was obtained from all study participants. Study participants were recruited consecutively from among patients with EHT who attended the outpatient hypertension clinic at Ehime University Hospital between October 2005 and September 2006. Essential hypertension was defined as the use of antihypertensive drugs at screening, systolic blood pressure (SBP) >140 mm Hg, or diastolic BP (DBP) >90 mm Hg expressed as the average of 3 measurements taken in the seated position using a brachial automated sphygmomanometer (HEM 9000-AI, Omron, Kyoto, Japan).

Patients with congestive heart failure, previous myocardial infarction, angina pectoris, atrial fibrillation, chronic renal failure (serum creatinine concentration >1.5 mg/dL), peripheral arterial disease (ankle-brachial index <0.9), or a history of stroke were excluded from the study. Patients taking antihypertensive drugs at screening entered a washout period of ≥2 weeks. Medications other than antihypertensive drugs were allowed to be continued, although no changes in these regimens were permitted during the study period.

After baseline measurements of blood pressure and CAVI were obtained, eligible patients were assigned to either the amlodipine or candesartan group. A pseudorandomization method was employed; patients with even medical record numbers were assigned to the amlodipine group and those with odd numbers were assigned to the candesartan group. Patients in the amlodipine group received 5 mg of amlodipine once daily and those in the candesartan group received candesartan 8 mg once daily as a starting dose. In patients whose blood pressure was not controlled after 4 weeks (SBP >140 mm Hg and/or DBP >90 mm Hg), the dose of amlodipine or candesartan was titrated to 10 or 12 mg, respectively. Evaluation of the patients, including blood pressure, heart rate, measurement of biochemical markers, and adverse events, was conducted every 4 weeks at the study visits. Compliance was also determined at this time. Outpatients were evaluated by the lead study investigator (M.K.) who was blinded to treatment. CAVI was remeasured at the end of the 24-week treatment period.
Measurement of Cardio-Ankle Vascular Index

The patients were placed in the supine position for $\geq 10$ minutes and then electrocardiography and phonocardiography were performed. $\text{baPWV}$ was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the difference between the time a pulse wave was transmitted to the brachium and the time the same wave was transmitted to the ankle, and the time difference between the second heart sound on phonocardiography and the notch of the brachial pulse waves ($\text{VaSera VS-1000; Fukuda Denshi, Tokyo, Japan}$). The formula used to calculate CAVI was as follows:

\[
\text{CAVI} = a \left( \frac{2p}{\Delta P} \times \ln \left( \frac{\text{SBP/DBP}}{\text{baPWV}^2} \right) \right) + b,
\]

where $p$ is blood density, $\Delta P$ is SBP - DBP, and $a$ and $b$ are constants to match aortic PWV according to the method of Hasegawa. This equation was derived from the Bramwell-Hill equation and the stiffness parameter. CAVI reflects the stiffness of the aorta and the femoral and tibial arteries as a whole and, theoretically, is not affected by blood pressure. These measurements and calculations were done automatically at the same time. BP was measured at the brachial artery. The average CV for the CAVI measurement has been reported to be 3.8%.

Statistical Analysis

All values are expressed as mean (SD). The baseline characteristics of the patients enrolled in the 2 treatment groups were compared using the unpaired $t$ test, the Mann-Whitney $U$ test, or the $\chi^2$ test. Changes in SBP, DBP, and CAVI between baseline and the end of the 24-week treatment period were analyzed using paired $t$ tests. Logistic regression analysis was carried out to determine the independent prescriptive factor for improvement in CAVI. The relative change in CAVI was analyzed by unpaired $t$ test. We defined a decrease in baseline CAVI after 24 weeks as state 1 and used study drug and $\Delta$SBP (treatment SBP - baseline SBP) as the covariants. A sample size of $\geq 25$ patients was considered sufficient. The odds ratios (ORs) were then calculated. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the Study Participants

Twenty patients (11 men, 9 women; mean [SD] age, 62 [10] years) were included in the study and evenly assigned to the 2 groups. All baseline demographic and clinical characteristics were similar between the 2 treatment groups (Table). In both groups, 3 patients were receiving $\beta$-blockers until 2 weeks before starting this study. One patient in the candesartan group was being treated with an antiplatelet drug. Three patients in the amlodipine group and 2 patients in the candesartan group had diabetes mellitus. No patients were withdrawn from the study for any reason, and no cardiovascular events were reported during the study.
### Table. Baseline demographic and clinical characteristics of outpatients with essential hypertension (N = 20).*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>Amlodipine (n = 10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Candesartan (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>61 (12)</td>
<td>62 (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (60)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (40)</td>
<td>5 (50)</td>
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<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>25.7 (4.9)</td>
<td>24.8 (2.4)</td>
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<td>Duration of hypertension, mean (SD), y</td>
<td>8 (4)</td>
<td>7 (5)</td>
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<tr>
<td>Diabetes mellitus, no. (%)†</td>
<td>3 (30)</td>
<td>2 (20)</td>
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<tr>
<td>Smoking status, no. (%)†</td>
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<tr>
<td>Current</td>
<td>2 (20)</td>
<td>2 (20)</td>
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<tr>
<td>Past</td>
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<tr>
<td>Never</td>
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<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
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<tr>
<td>Systolic</td>
<td>150 (17)</td>
<td>152 (18)</td>
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<tr>
<td>Diastolic</td>
<td>93 (13)</td>
<td>91 (15)</td>
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<tr>
<td>Pulse§</td>
<td>59 (13)</td>
<td>60 (15)</td>
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<td>Drug treatment, no. (%)†</td>
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</tr>
<tr>
<td>Antiplatelet</td>
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<td>1 (10)</td>
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<td>Statin</td>
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<td>0</td>
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<td>Other antihypertensive drugs</td>
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<td>3 (30)</td>
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<td>Total cholesterol, mean (SD), mg/dL</td>
<td>202 (40)</td>
<td>216 (31)</td>
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<tr>
<td>Triglyceride, mean (SD), mg/dL</td>
<td>123 (35)</td>
<td>113 (57)</td>
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<td>HDL-C, mean (SD), mg/dL</td>
<td>58 (17)</td>
<td>54 (14)</td>
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<tr>
<td>Creatinine, mean (SD), mg/dL</td>
<td>0.73 (0.21)</td>
<td>0.74 (0.17)</td>
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<tr>
<td>FPG, mean (SD), mg/dL</td>
<td>102 (9)</td>
<td>106 (29)</td>
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<tr>
<td>Hemoglobin A₁c, mean (SD), %</td>
<td>5.34 (0.59)</td>
<td>5.59 (0.78)</td>
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<td>Urine albumin/creatinine ratio, mean (SD)</td>
<td>21.7 (20.5)</td>
<td>18.7 (11.4)</td>
</tr>
<tr>
<td>ECG voltage, mean (SD), sV1 + RV5, mV</td>
<td>3.23 (1.19)</td>
<td>2.84 (0.88)</td>
</tr>
<tr>
<td>PWV, mean (SD)</td>
<td>1515 (259)</td>
<td>1561 (278)</td>
</tr>
<tr>
<td>CAVI</td>
<td>8.93 (0.93)</td>
<td>8.46 (1.34)</td>
</tr>
</tbody>
</table>

**HDL-C** = high-density lipoprotein cholesterol; **FPG** = fasting plasma glucose; **ECG** = electrocardiographic; **PWV** = pulse wave velocity; **CAVI** = cardio-ankle vascular index.

*No significant between-group differences were found.
† Mann-Whitney U test.
‡ Kruskal-Wallis test.
§ Determined as systolic blood pressure minus diastolic blood pressure.
EFFECTS OF ANTIHYPERTENSIVE THERAPY ON BLOOD PRESSURE
SBP and DBP decreased significantly in both treatment groups (Figure 1). At the end of 24 weeks of treatment, the mean reductions in SBP, DBP, and pulse pressure in the amlodipine group were 14, 10, and 7 mm Hg \( (P = 0.006, 0.005, \text{ and } 0.139, \text{ respectively}) \) and in the candesartan group were 13, 11, and 2 mm Hg \( (P = 0.033, 0.005, \text{ and } 0.799, \text{ respectively}) \). Reductions in SBP, DBP, and pulse pressure were not significantly different between the 2 treatment groups.

CHANGES IN ARTERIAL COMPLIANCE AS MEASURED BY CARDIO-ANKLE VASCULAR INDEX
At baseline, CAVI was not significantly different in the amlodipine group compared with the candesartan group \( (8.93 \pm 0.93\text{ vs } 8.46 \pm 1.34, \text{ respectively}) \). After
24 weeks of treatment, CAVI was decreased significantly from baseline in the amlodipine group (8.60 [1.50]; \( P = 0.017 \); decreased in 8 patients), whereas it did not change significantly in the candesartan group (8.81 [1.20]; decreased in 2 patients) (Figure 2). The percentage change in CAVI was significantly different in the amlodipine group compared with the candesartan group (\(-7.14 [8.83] \) vs \( 5.85 [16.0] \), respectively; \( P = 0.038 \)). There was no significant difference between the 2 groups in absolute CAVI after 24 weeks of treatment. Logistic regression analysis with adjustment for ΔSBP, baseline CAVI, and study drugs revealed that amlodipine improved CAVI (OR, 18.37; 95% CI, \( 1.399-2.412 \); \( P = 0.027 \)) independent of its SBP-lowering effects (OR, 0.940; 95% CI, \( 0.862-1.025 \)) and baseline CAVI (OR, 1.290; 95% CI, \( 0.464-3.585 \)).

**DISCUSSION**

We found that aortic stiffness measured by CAVI improved from baseline after 24 weeks of treatment; both drugs reduced SBP and DBP to the same extent. There was no significant difference in absolute CAVI after 24 weeks of treatment between the 2 groups, although the relative change from baseline in CAVI significantly favored the amlodipine group.

The reduction in compliance of the aorta and elastic arteries has been found to be a strong independent predictor of cardiovascular events and death.\(^3\)\(^-\)\(^5\) Laurent et al\(^2\) found that arterial stiffness evaluated by cfPWV was significantly associated with the occurrence of all cardiovascular events after adjustment for the Framingham Risk Score in the cohort study. In a prospective cohort study by Benetos et al,\(^24\) the rate of PWV progression was reported to be higher in patients with hypertension than in normotensive subjects, after adjustment for age, sex, and initial PWV values (171 [20] vs 66 [16] mm/s · y\(^{-1}\); \( P < 0.001 \)). They also reported that hypertensive patients whose blood pressure was well controlled during a 6-year follow-up period had a rate of PWV progression lower than that of hypertensive patients whose blood pressure was not well controlled.
progression similar to that of normotensive subjects (49 [40] vs 81 [18] mm/s · y⁻¹, respectively), suggesting that blood pressure control is important for attenuating the hypertension-related progression of arterial stiffness.²⁴

We found arterial stiffness, evaluated by CAVI, was significantly improved in amlodipine-treated patients, but not in patients receiving candesartan, despite the blood pressure–lowering effect being similar with the 2 treatments. Logistic regression analysis showed that the improvement in CAVI in the amlodipine group was independent of its blood pressure–lowering effect. These results suggest that factors other than blood pressure are involved in increased arterial stiffness in hypertensive patients and that amlodipine may prevent arterial stiffening, at least in part, by attenuating blood pressure–independent mechanisms.

Amlodipine has been reported to have pleiotropic effects beyond its blood pressure–lowering action.¹⁹⁻²¹ Amlodipine has both antioxidative and antiproliferative effects on vascular smooth muscle cells and also enhances nitric oxide production by vascular endothelial cells. The beneficial effects of these blood pressure–independent pleiotropic effects of amlodipine have been reported in clinical studies. In the CAMELOT (The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis) study,¹⁸ a multicenter, prospective, randomized, open, blinded end point study, administration of amlodipine for 24 months to normotensive patients with coronary artery disease resulted in a reduction in adverse cardiovascular events, whereas no significant treatment effects were observed with enalapril. Furthermore, the assessment of atherosclerotic plaques by intravascular ultrasonography showed no progression in plaque volume in patients receiving amlodipine.²⁵ These results indicated that not only ARBs, but also amlodipine may have antiatherosclerotic effects.

Previous studies have reported that ARBs improve aortic stiffness estimated by baPWV in hypertensive patients; our findings were inconsistent with these studies.²⁶⁻²⁸ ARBs also have been reported to have pleiotropic effects, such as antioxidative and antiatherogenic effects.²⁸,²⁹ Candesartan did not improve CAVI at 24 weeks of treatment. Another reason why candesartan did not reduce CAVI as much as amlodipine may be due to study duration. Twenty-four weeks may be too short to demonstrate the pleiotropic effect of an ARB. Our findings, taken together with the findings of previous studies, suggest that amlodipine may attenuate hypertension-related arterial stiffening through both blood pressure–dependent and –independent mechanisms, whereas the effects of candesartan appeared weaker than amlodipine at 24 weeks.

CAVI has been reported to be useful in evaluating arteriosclerosis and atherosclerosis.³⁰ Wakabayashi and Masuda³¹ reported acute-phase reactants, such as C-reactive protein, serum amyloid A, sialic acid, fibrinogen, and leukocyte count (correlation coefficients: 0.214 [P < 0.05]; 0.261 [P < 0.01]; 0.308 [P < 0.001]; 0.300 [P = 0.001]; and 0.194 [P < 0.05]), were associated with CAVI in patients with type 2 diabetes mellitus. We also reported a strong correlation between CAVI and carotid arteriosclerosis or stiffness in patients with EHT.¹¹ Therefore, our current finding that treatment with amlodipine for 24 weeks improved CAVI suggests that amlodipine may have beneficial effects on atherosclerosis in these hypertensive patients.
Limitations

The findings were obtained using a small number of patients who were treated for a relatively short duration. We did not meet the sample size of ≥25 subjects, which was determined to be adequate for the analysis. Kubozono et al reported that the mean (SD) CAVI of 1033 consecutive Japanese subjects who were undergoing health evaluations was 8.3 (1.4). In the present study, the CAVI was reduced to 8.60 (1.5) after treatment with amlodipine, which was similar to the CAVI in the Japanese cohort. We could not exclude the effect of concomitant drugs, such as antiplatelet drugs, although there were no significant differences in medications between the amlodipine and candesartan groups at baseline and these medications were not changed during the study. We used the patients’ medical record numbers to assign them to treatment, and this was an open-label trial. Larger, longer, double-blind, randomized controlled trials are necessary to confirm these findings. There was the possibility of introducing bias by having the same investigator assess the study outcomes. After 24 weeks of treatment, the CAVI of the amlodipine group was still numerically larger than the baseline CAVI of the candesartan group, although the difference was not statistically significant. Furthermore, there was no significant difference in absolute CAVI between the 2 groups after 24 weeks, but the relative change was significant in favor of amlodipine. Finally, because CAVI is a relatively new tool to estimate arterial stiffness, whether it can be used to predict clinical outcomes remains unknown. However, CAVI seems to correlate well with measures of hypertensive target organ damage, such as carotid arterial intima-media thickness and left ventricular diastolic function.

Conclusion

These data suggest that amlodipine and candesartan had different effects on aortic stiffness estimated by CAVI, despite similar effects on brachial blood pressure after 24 weeks of treatment in these Japanese patients with EHHT. Larger, longer-term, randomized studies are needed to evaluate the effect of amlodipine on CAVI.

References


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