Original Article

Selective Angiotensin Receptor Antagonism with Valsartan Decreases Arterial Stiffness Independently of Blood Pressure Lowering in Hypertensive Patients

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Angiotensin II plays a key role in the development of vascular disease. We examined the long-term effects of selective angiotensin II receptor (ATR) blockade with valsartan on arterial wall stiffness. Brachial to ankle pulse wave velocity (baPWV) was measured in 28 women and 25 men with hypertension (mean age: 62±2 years). The measurements were repeated after 24 weeks of treatment with valsartan, 40 to 160 mg/day, with (*n*=10) or without (*n*=36) concomitant statin therapy. By multiple regression analysis, baseline baPWV was correlated with age ($p<0.001$), systolic blood pressure (SBP, $p<0.0001$), body mass index ($p=0.018$), and pulse pressure ($p=0.005$), but not with total cholesterol ($p=0.446$). Valsartan lowered mean SBP and diastolic blood pressure (DBP) from 155±3 to 140±3 mmHg and from 90±2 to 82±2 mmHg, respectively, and mean baPWV from 1,853±49 to 1,682±52 cm/s. Lowering of baPWV was not influenced by statin therapy. An overlap analysis was performed to separate the effect of angiotensin II receptor blockade from that of blood pressure (BP) lowering. The decrease in the baPWV value of 1,794±46 cm/s before valsartan (*n*=39) *vs.* 1,663±45 cm/s during valsartan ($p=0.048$, *n*=31) at a similar mean SBP level (149±2 *vs.* 146±3 mmHg, $p=0.304$) confirmed that ATR blockade had a beneficial effect independent of BP lowering. SBP strongly influences baPWV. However, the decrease in baPWV with valsartan was independent of BP lowering. Statins had no synergistic effect on baPWV. Lowering of baPWV may account for the therapeutic benefit conferred by valsartan independent of its BP-lowering effect. (*Hypertens Res* 2005; 28: 937–943)

***Key Words*: pulse wave velocity, statin, anti-hypertensive therapy**

Introduction

Angiotensin II, a hormone with hemodynamic and renal actions, is also a locally active biologic mediator which has direct effects on endothelial and vascular smooth muscle cells (VSMC) and plays a key role in the initiation and amplification of abnormal biological events leading to the development of vascular disease (*1*). Angiotensin II is a major mediator of oxidative stress and reduced nitric oxide activity by activation of NADH/NADPH oxidase, which results in the production of the superoxide anion (*2*). Angiotensin II may also promote vascular remodeling and formation of vascular lesions by modulating the migration of VSMC (*3*), decreasing VSMC apoptosis (*4*) and inducing an accumulation of vascular collagen (*5*), suggesting that it is a pleiotropic local mediator. These major cardiovascular effects are mediated by the type 1 angiotensin II receptor (ATR). We have previously reported

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Table 1. Baseline Characteristics and Drug Regimen Administered in the Study Population (n=53)

Men/women (n)	25/28
Age (years)	62.0±1.5 (87–88)
Blood pressure (mmHg)	
Systolic	159±3 (125–222)
Diastolic	91±2 (68–120)
Body mass index (kg/m^2)	24.9±0.5 (19.7–40.4)
Serum creatinine (mg/dl)	0.80±0.03 (0.47–1.50)
Serum cholesterol (mg/dl)	
Total	214±4 (133–280)
HDL	56±2 (33–93)
Serum uric acid (mg/dl)	5.1±0.2 (3.1–8.9)
Baseline drug regimen	
Statin	7
Clofibrate	3
Diuretics	1
Aspirin	1
Other antiplatelet agent	2
Calcium channel blocker	18
α-Adrenergic blocker	2
β-Adrenergic blocker	2
None	28

Unless specified otherwise, values are means±SD (range). HDL, high-density lipoprotein.

Table 2. Independent Predictors of Brachium-Ankle Pulse Wave Velocity by Multiple Regression Analysis

	β	t value	p value
Age	11.970	3.714	0.00064
Systolic blood pressure	15.341	5.041	0.00001
Body mass index	22.793	2.460	0.01842
Pulse pressure	13.607	2.969	0.00509
Total cholesterol	0.923	0.770	0.44602

Multiple r^2=0.409, p<0.0001.

that angiotensin II receptor blockade protects endothelial function in renal hypertension (*6*), and type 1 angiotensin II receptor blockers (ARB) have now been widely used as antihypertensive drugs with the expectation of a vascular protective effect (*7*).

Pulse wave velocity (PWV) is positively correlated with arterial wall stiffness, such that increased stiffness is associated with a greater arterial PWV. Aortic stiffness, which in hypertensive patients has been measured non-invasively by PWV along the aorto-iliac pathway, predicts all-cause and cardiovascular mortality (*8–11*). Aortic stiffness assessed by carotid-femoral PWV is strongly associated with atherosclerosis of the aorta, and carotid and peripheral arteries (*12*), and monitoring of PWV along the aortic pathway is useful to 1) evaluate the degree of atherosclerosis and 2) predict all-cause and cardiovascular mortality. While acutely lowering the blood pressure (BP) should delay the transmission of the pulse wave through the arterial vessel and decrease PWV, to our knowledge, whether long-term therapy with an ARB in patients with hypertension can further normalize PWV remains unclear.

The present study examined the long-term effects of valsartan, a selective ARB, on the arterial wall stiffness of hypertensive patients.

Methods

We recruited 53 consecutive hypertensive patients from the Gunma University Hospital or affiliated institutions. The Ethics Review Board of Gunma University Hospital approved the study protocol, and informed consent was obtained from all patients. Hypertension was defined as a systolic BP (SBP) >140 mmHg or diastolic BP (DBP) >90 mmHg, measured by sphygmomanometry. Patients with secondary hypertension, based on the results of standard laboratory and radiology tests, and patients treated with angiotensin-converting enzyme inhibitors or an ARB in the past 6 months were excluded from the study. Patients previously treated with calcium channel blockers, α- or β-adrenergic blockers, or diuretics, alone or in combination, were not excluded from the study. Important baseline demographic, clinical and treatment characteristics of the study population are shown in Table 1.

Baseline Measurements

Arterial wall stiffness was measured by PWV between the brachium and ankle (baPWV). The PWV measurements, along with the heart rate (HR) and BP measurements, were made with a model BP-203RPE pulse pressure analyzer (Nihon Colin, Tokyo, Japan) by previously described methods (*13*, *14*). Briefly, pulse volume waveforms were recorded with plethysmographic sensors placed on the right brachial and on both posterior tibial arteries. Based on the phase velocity theory, which states that the mean value of the phase velocity >2–2.5 Hz approximates the wave front (*15*), the latter was automatically measured by using the components >5 Hz through a pass filter. Electrocardiograms were recorded with 2 electrodes placed on the left and 1 electrode on the right arm. The time between the wave front at the brachial level and the posterior tibial wave front was recorded as the time interval between the brachium and ankle. The distance between the right brachial and posterior tibial artery was derived from the patient's measurements. baPWV was measured after at least 3 min of rest, during stable HR between 60 and 80 bpm. The averages of 2 measurements (in cm/s) in each leg were used for the analysis. Venous blood for the measurements of total cholesterol was collected after an over-

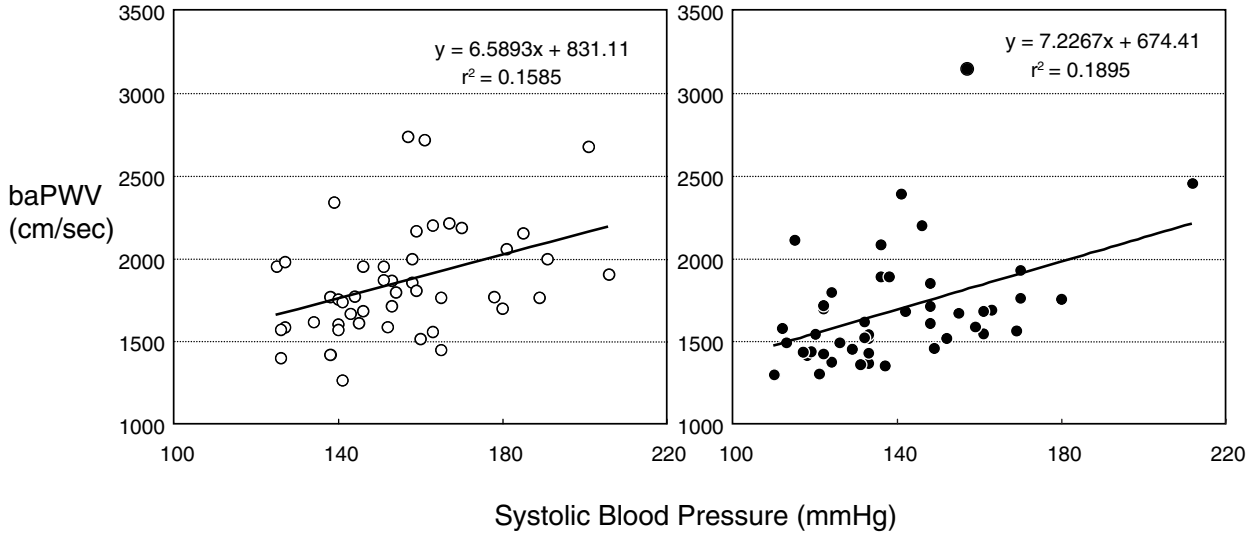

Fig. 1. *Correlation of systolic blood pressure (SBP) with brachial-ankle pulse wave velocity (baPWV). Open and closed circles represent the data points before and during treatment with valsartan, respectively.*

night fast in the morning of the PWV measurements.

Effect of Long-Term Treatment with Valsartan on Arterial Stiffness

The prospective study included 46 of the 53 patients in whom baseline arterial stiffness was measured. After collection of the baseline measurements, all patients were placed on a treatment of valsartan, 40 to 160 mg/day. Angiotensin-converting enzyme inhibitors or ARBs other than valsartan were not administered during the study. The patients' physicians were unaware of baPWV measurements during the 6-month treatment period. We also compared the baPWV measurements between 10 patients treated with and 36 patients not treated with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin). In a subgroup of 19 patients, baPWV was measured every 8 weeks.

Statistical Analyses

Data are expressed as the mean±SEM. Multiple regression analysis was performed among the values of age, body mass index (BMI), SBP, pulse pressure, total serum cholesterol and baPWV at baseline in the 53 patients. The analysis was first performed to examine the association between baPWV and other clinical variables. Step-wise multiple regression analysis was then performed to identify variables independently associated with baPWV.

The relationship between SBP and baPWV was examined by Pearson correlation coefficients for continuous variables. Comparison of baPWV in patients before and during valsartan treatment with the same BP level was analyzed using an overlap analysis of SBP and baPWV (*16*). Investigation of the SBP distribution in these patients was expected to reveal that the range between 125 and 169 mmHg encompassed a high proportion of patients who had overlapping SBP values either before or during treatment with valsartan. The mean baPWV values before and during treatment with valsartan in this overlapping range of SBP were compared by Student's *t*-test. χ^2 test was also used to compare gender distributions.

The changes in biological parameters and their differences between the groups treated with or without a statin were analyzed by two-way analysis of variance for repeated measures combined with the Newman-Keuls *post hoc* test. One-way analysis of variance was also used to analyze the data of longitudinal observation of BP and baPWV. A p value <0.05 was considered statistically significant.

Results

Independent Predictors of baPWV

Table 2 shows the results of the multiple regression analysis with respect to baseline variables in the 53 patients. By multiple regression analysis, baseline baPWV was correlated with age ($p<0.001$), SBP ($p<0.0001$), BMI ($p<0.05$), and pulse pressure ($p<0.01$), but not with total cholesterol ($p=0.45$).

Effect of Long-Term Treatment with Valsartan on baPWV

Valsartan lowered SBP and DBP from 155±3 to 140±3 mmHg, and from 90±2 to 82±2 mmHg, respectively. HR averaged 72±1 bpm at baseline and was unchanged after the 24-week treatment period. By regression analysis, baPWV was correlated with SBP at baseline ($y=6.5893x + 831.11$,

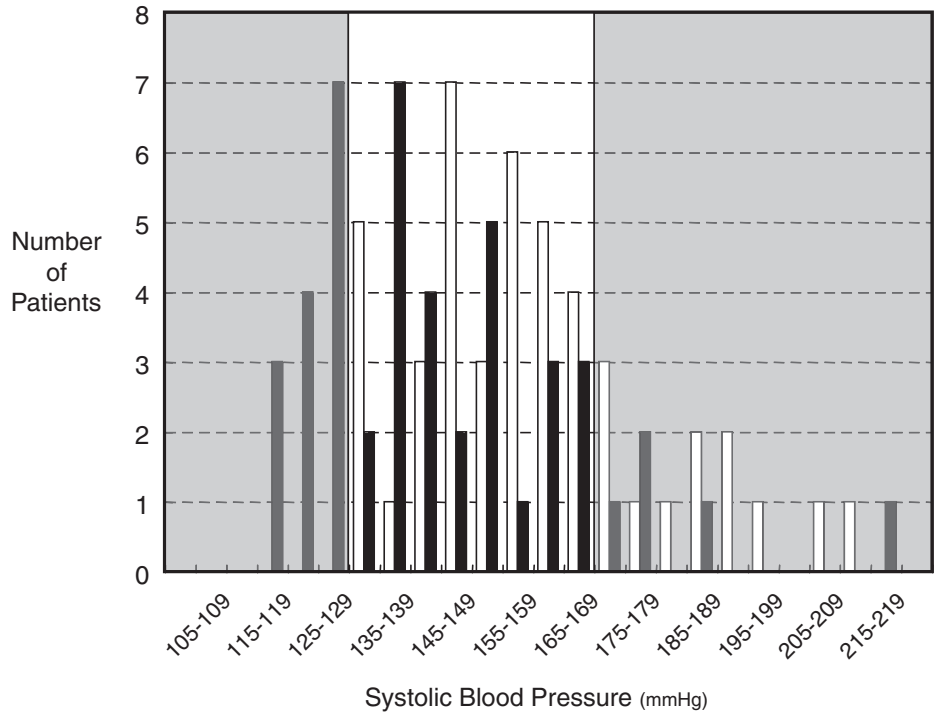

Fig. 2. *Overlap analysis. Frequency distribution of systolic blood pressure is shown as separate histograms before and during treatment with valsartan for 24 weeks. Open and closed bars represent the data before and during treatment with valsartan, respectively. An overlap range between 125 mmHg and 169 mmHg was chosen to include sufficiently prevalent values in both treatment phases.*

Table 3. Effects of Valsartan on baPWV in Patients Whose Systolic Blood Pressure Overlapped Both before and during Treatment

	Before valsartan (n=39)	During valsartan (n=31)	p
baPWV (cm/s)	1,794±46	1,663±45	0.048
Men/women (n)	17/22	15/16	0.689
Age (yeas)	63±2	60±2	0.134
Systolic blood pressure (mmHg)	149±2	146±3	0.304
Diastolic blood pressure (mmHg)	87±2	85±2	0.431
Body mass index	25.0±0.5	24.8±0.6	0.854
Total cholesterol (mg/dl)	216.1±5.5	204.5±6.5	0.182
Serum creatinine (mg/dl)	0.80±0.03	0.80±0.05	0.979

Unless specified otherwise, data are means±SEM. The frequency distribution of systolic blood pressure during treatment is shown on separate histograms in Fig. 2. baPWV, brachium-ankle pulse wave velocity.

r^2=0.1585, p<0.0001, Fig. 1) and after 24 weeks (y=7.2267x + 674.41, r^2=0.1895, p<0.0001, Fig. 1) of treatment with valsartan. Valsartan also lowered baPWV significantly from 1,853±49 cm/s at baseline to 1,682±52 cm/s after 6 months of valsartan administration.

Comparison of baPWV in Patients within the Same BP Range before and during Treatment with Valsartan

Figure 2 shows a leftward-shifted scattergram of the SBP before *vs*. during treatment with valsartan. The distributions overlapped substantially, with 70 values included within the range between 125 and 169 mmHg. This allowed us to further explore the relationship between SBP and baPWV with

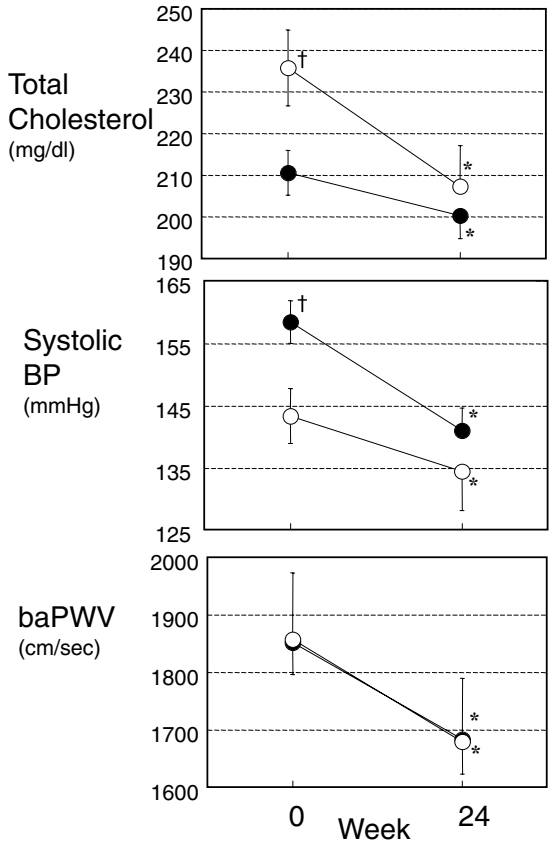

Fig. 3. *Comparison of the effects of treatment with valsartan on brachial-ankle pulse wave velocity (baPWV) between patients treated with (open circles) and those treated without (closed circles) concomitant statin. Data are reported as the means±SEM.* *p*< 0.05* vs. *baseline.* †p*< 0.05* vs. *absence of concomitant treatment with statin.*

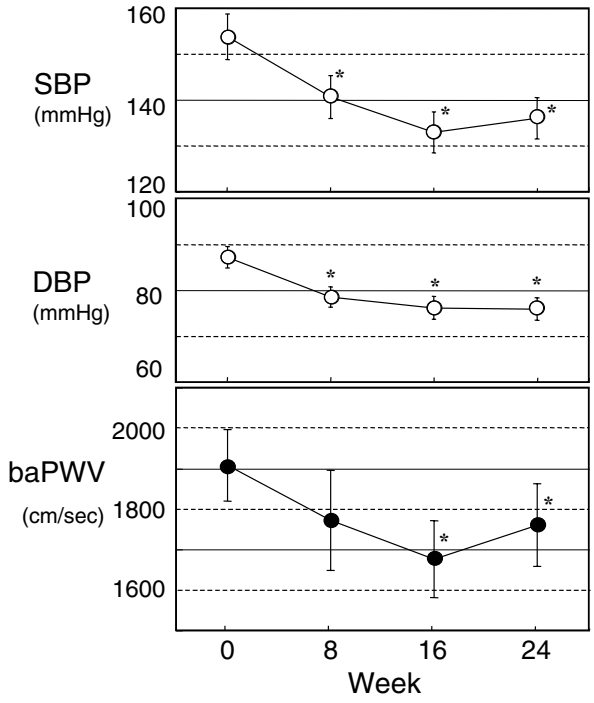

Fig. 4. *Changes in systolic (SBP) and diastolic blood pressures (DBP) and brachial-ankle pulse wave velocity (baPWV) every 8 weeks, during the 24-week treatment period with valsartan. Data are reported as the mean±SEM.* *p*< 0.05* vs. *baseline.*

respect to treatment with valsartan. Mean baPWV within this range was 1,794±46 cm/s before treatment (n=39) *vs.* 1,663±45 cm/s (n=31) during treatment (p=0.048, Table 3). Other variables were not significantly different (Table 3).

Effects of Statins

In the 10 patients treated and the 36 patients not treated with a statin, SBP decreased significantly (Fig. 3). Likewise, significant decreases in total serum cholesterol were observed in patients treated with (from 236±9 to 207±10 mg/dl, p<0.05) and patients not treated with a statin (from 211±5 to 200±6 mg/dl, p<0.05). Finally, over the 24-week period of treatment, baPWV decreased in patients treated with a statin, from 1,857±116 to 1,680±110 cm/s (p<0.05), while it decreased from 1,852±56 to 1,684±60 cm/s (p<0.05) in untreated patients. There was no significant difference in baPWV changes between patients treated and those not treated with a statin (Fig. 3).

Longitudinal Observation of BP and baPWV

Figure 4 shows the mean SBP and DBP and baPWV in the subgroup of 19 patients who underwent measurements at baseline and every 8 weeks during treatment with valsartan. Mean baseline SBP and DBP were 154±5 and 86±3 mmHg, respectively. SBP and DBP both decreased significantly to 141±4 and 78±2 mmHg, respectively, at 8 weeks of therapy. In contrast, the change in baPWV (from 1,980±89 cm/s at baseline to 1,772±127 cm/s at 8 weeks) was not significant. baPWV was significantly lower at 16 weeks (1,676±95 cm/s, p<0.05) and 24 weeks (1,760±102 cm/s, p<0.05) than at baseline.

Discussion

The results of this study demonstrate that long-term BP treatment with an ARB, valsartan, decreased baPWV significantly. In the overlap analysis, while BP was nearly the same, baPWV was significantly lower during treatment. This is the first report which shows that ATR blockade with valsartan during a treatment period of as long as 24 weeks progressively decreased baPWV, separately from its BP-lowering effect, in hypertensive patients. Treatment with valsartan may cause beneficial structural modifications in the arterial wall,

regardless of the level of SBP.

A recent study demonstrated the accelerated progression of aortic stiffness during a 6-year follow-up of 187 treated hypertensive patients, in whom a mean BP of 150/87 mmHg was reached by anti-hypertensive therapy (*17*). Therefore, BP may have to be lowered more vigorously to prevent the development of arterial wall stiffness. In the subgroup of 19 patients whose baPWV was measured every 8 weeks in our study, both SBP and baPWV decreased as early as 16 weeks of treatment. This observation suggests that vigorous lowering of BP to the level of 140/90 mmHg reached in the present study significantly decreases baPWV in hypertensive patients. Furthermore, sustained angiotensin II receptor blockade for 24 weeks significantly enhanced the decrease in baPWV in response to BP lowering. This observation is consistent with the report of a significant slowing of the progression of aortic atherosclerosis by long-acting ARB (*18*). In a recent study, treatment with valsartan limited to 3 months in duration was more effective in decreasing baPWV than the calcium channel blocker, nifedipine (*19*).

The relationship between baPWV and SBP between 125 and 169 mmHg was linear, before and during treatment with valsartan (Fig. 1). Although acute lowering of BP is known to delay the pulse wave transmission through the arterial vessel and decrease baPWV, it may also activate autonomic nervous and renal compensatory mechanisms and inhibit the decrease in baPWV. In the present study, SBP was lowered significantly as early as 8 weeks, though baPWV was not significantly decreased at that point (Fig. 4). Over the shorter-term, the anti-hypertensive effect may cause fluctuations in BP and excessive tension in the arterial wall, perhaps by activating the sympathetic nervous system. Because the degree of BP lowering in the present study was not markedly more pronounced than in other studies (*14*, *17*), we hypothesize that vigorous BP lowering with an ARB can overwhelm the compensatory mechanisms and cause a significant decrease in baPWV.

Although PWV reflects the functional and anatomic states of arterial wall elasticity, the results of our study suggest that the latter can be improved by intensive BP lowering to near normal levels plus angiotensin II receptor blockade, sustained for at least 24 weeks. This is particularly important, since previous studies have shown that PWV predicts cardiovascular mortality and morbidity in hypertensive patients (*8–11*). baPWV can, therefore, be used as an indicator of the degree of vascular protection during long-term anti-hypertensive treatment.

Age (*20*, *21*), gender (*22*), serum lipids levels (*23*), renal function (*24*), SBP (*22*), pulse pressure (*25*), HR (*26*) and other cardiovascular risk factors (*27–29*) may influence baPWV and its progression in hypertensive patients and normotensive subjects. The results of the present study were partially consistent with those of previous studies, and established significant correlations between baseline baPWV and age, BMI, SBP and pulse pressure. However, baPWV was not correlated with serum total cholesterol. Furthermore, no significant difference in baPWV was observed between patients treated and those not treated with a statin. Two recent studies (*30*, *31*) also reported finding no significant correlation between PWV and serum total cholesterol. In the present study, although patients treated with a statin showed a marked decrease in mean total cholesterol concentration, as well as a significant decrease in baPWV, no significant difference in baPWV was observed between patients treated and those not treated with a statin. These results failed to show a prominent contribution of statin in the achievement of a decrease in baPWV. Ichihara *et al*. also reported recently that the statins they tested were ineffective in decreasing PWV in hypertensive patients (*32*). They showed that only fluvastatin, a statin with antioxidant activity, improved PWV. Therefore, the therapeutic benefit is likely to be mostly attributable to BP lowering and angiotensin II receptor blockade.

In summary, our study suggests that intensive angiotensin II receptor blockade has beneficial effects on arterial wall stiffness in hypertensive patients. The decrease in baPWV with valsartan may explain the lower rate of cardiovascular events, and, consequently, the higher event-free survival observed with ATR blockade independent of its anti-hypertensive effects.

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