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Fluvastatin Improves Arterial Stiffness in Patients With Coronary Artery Disease and Hyperlipidemia

—— A 5-Year Follow-up Study ——

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Background The present study was designed to test the hypothesis that fluvastatin might improve arterial stiffness, as assessed with pulse wave velocity (PWV), in patients with coronary artery disease (CAD) and hyperlipidemia over the long term.

Methods and Results Ninety-three patients were randomly assigned to either fluvastatin (group A, n=50) or bezafibrate (group B, n=43) and followed for 5 years. There was no difference in the clinical findings between the 2 groups. In group A, there was a progressive reduction in the brachial-ankle PWV along with a decrease in serum low-density lipoprotein-cholesterol (LDL-C) and C-reactive protein (CRP) by 12 months after fluvastatin, and the improvement was maintained until 5 years after treatment. In group B, despite identical lowering of the serum lipid, PWV was progressively increased. In group A, the percentage change in PWV correlated significantly with that of the serum CRP (r=0.49, p<0.001), but not with that of the serum LDL-C after treatment.

Conclusions The beneficial vascular effects of fluvastatin persisted for a long period in patients with CAD and hyperlipidemia. Its anti-inflammatory action might contribute to the favorable effects on arterial stiffness. (*Circ J* 2008; **72:** 722–728)

Key Words: Arterial stiffness; Coronary artery disease; Fluvastatin; Long-term follow-up

Measurements of pulse wave velocity (PWV) are useful for evaluating aortic stiffness, which has been shown to be associated with traditional risk factors[1–5] Aortic stiffness, but not stiffness of peripheral muscular arteries, also has been noted to predict not only primary coronary events and fatal stroke in a variety of disease conditions, such as end-stage renal disease[6] hypertension[7] and diabetes[8] but also cardiovascular mortality in the general population[9–11] Although conventional techniques for measuring carotid-femoral PWV are non-invasive, sophisticated methods, they are inconvenient, particularly in large clinical trials. Recently, brachial-ankle (ba) PWV has been developed as a more simple, practical, reproducible procedure to assess both the central elastic and peripheral muscular arterial stiffness[12,13] It has been reported that the baPWV is closely correlated with aortic PWV and leg PWV,[13] is associated with risk factors and organ damage in the presence of cardiovascular diseases[14–16] and has a prognostic value for future cardiovascular events in patients with acute coronary syndrome[17] Thus, the measurement of baPWV is suitable, especially for screening vascular damage in a large population and when assessing vascular damage in long-term follow-up studies.

Recent studies suggest that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (ie, statins) act to exert direct beneficial effects on myocardial ischemia and hypertrophy, coronary vasomotion and vascular smooth muscle cell proliferation, and reduce adverse cardiovascular events in patients at risk through not only the lipid-lowering action but also the lipid-independent anti-atherogenic properties; that is, the so-called pleiotropic effects. Although fluvastatin, but not pravastatin or non-statin antihyperlipidemic agents, has been noted to improve aortic stiffness in association with decreased serum lipid and C-reactive protein (CRP) levels over a treatment period of 12 months,[18] its effect over longer treatment periods has not yet been clarified. Thus, the present study was designed to test the hypothesis that fluvastatin might improve arterial stiffness assessed by PWV in patients with coronary artery disease (CAD) and hyperlipidemia over a much longer treatment period. We also investigated whether arterial stiffness improved in patients whose drugs had been switched from non-statin antihyperlipidemic agents to fluvastatin.

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Methods

Protocol 1

Subjects and Study Protocol Patients with CAD and hyperlipidemia who visited the outpatient clinic of the Department of Cardiovascular Medicine, Shinshu University Hospital between April 2000 and August 2001 were enrolled

Table 1 Clinical Characteristics in Protocol 1

	Group A		Group B	
	Initial	Final	Initial	Final
Number	50	50	43	43
Age (years)	69.3±9.5		69.6±9.4	
Gender (M/F)	21/29		18/25	
BMI (kg/m^2)	23.8±2.4	23.9±2.7	23.4±3.1	23.8±3.5
Systolic BP (mmHg)	130±14	131±15	132±16	135±20**,***
Diastolic BP (mmHg)	78±13	79±15	77±11	78±15
Heart rate (beats/min)	65±9	66±11	68±11	67±10
LV fractional shortening (%)	33±5	34±7	34±6	35±7
Number of CA lesions	1.8±0.8		1.9±0.9	
Risk factors				
Hypertension (%)	22 (44)	23 (46)	23 (53)	26 (60)**,***
Diabetes (%)	14 (28)	15 (30)	15 (35)	17 (40)
FPG (mg/dl)	92±13	91±16	92±14	95±17**,***
Hemoglobin A_{1c} (%)	6.2±1.3	6.1±1.6	6.2±1.5	6.4±1.7**,***
Serum TC (mg/dl)	245±36	212±28*	243±38	214±32*
Serum LDL-C (mg/dl)	157±16	127±15*	155±18	129±19*
Serum HDL-C (mg/dl)	42±6	40±4	41±5	40±4
Serum TG (mg/dl)	175±39	163±38*	173±37	161±39*
Hyperuricemia (%)	7 (14)	8 (16)	7 (16)	8 (19)
Smoking (%)	4 (8)	4 (8)	3 (7)	3 (7)
Other drugs				
ACEIs/ARBs (%)	20 (40)	22 (44)	20 (47)	25 (58)**,***
CCBs (%)	28 (56)	29 (58)	26 (60)	28 (65)***
β-blockers (%)	6 (12)	6 (12)	3 (7)	2 (5)
α-blockers (%)	7 (14)	6 (12)	5 (12)	6 (14)
Diuretics (%)	5 (10)	6 (12)	5 (12)	6 (14)
Aspirin (%)	41 (82)	42 (84)	35 (81)	36 (84)
baPWV	1,808±328	1,653±321*	1,806±358	2,005±429**,***
ABI	1.14±0.07	1.13±0.09	1.13±0.09	1.12±0.10
Serum hsCRP (mg/L)	1.78±0.36	1.24±0.29	1.80±0.41	1.82±0.40***
(range)	(1.06–3.15)	(0.89–2.26)	(0.89–3.44)	(1.28–3.71)

*$p<0.05$ vs initial examination in group A; **$p<0.05$ vs initial examination in group B; ***$p<0.05$ vs final examination in group A. Data are presented as numbers or as the mean±SD.
BMI, body mass index; BP, blood pressure; LV, left ventricular; CA, coronary artery; FPG, fasting plasma glucose; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglyceride; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; baPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial pressure index; hs, high-sensitivity; CRP, C-reactive protein.

in a prospective, randomized, single-blind, single-center study. Patients were enrolled in the study if they fulfilled the following inclusion criteria: (1) Presence of organic or functional CAD diagnosed by coronary angiography; (2) Presence of hyperlipidemia with serum total cholesterol (TC) ≥220 mg/dl, triglycerides (TG) ≥150 mg/dl or both; (3) Receiving no treatment with antihyperlipidemic agents, such as statins, bezafibrate and probucol; (4) Absence of sustained systolic and diastolic blood pressures (BP) at rest (ie, >180 mmHg and/or 100 mmHg) despite antihypertensive medication; (5) Absence of chronic diseases, such as peripheral arterial disease (ankle-brachial pressure index (ABI) <0.9), liver dysfunction, renal failure, inflammation and cerebrovascular diseases; and (6) Absence of atrial fibrillation.

Ninety-three patients were randomly assigned to receive either 20–40 mg/day of fluvastatin (group A) or the non-statin antihyperlipidemic drug (200–400 mg/day of bezafibrate) (group B), and were followed for 5 years. Group A comprised 50 patients (21 men and 29 women, aged 51–79 years, mean 69.3±9.5 years) and group B comprised 43 patients (18 men and 25 women, aged 50–80 years, mean 69.5±9.6 years). Upon inclusion in the study, medical records of the eligible patients were reviewed. Body mass index (BMI) was calculated and the presence of other atherosclerotic risk factors, including hypertension, diabetes mellitus, hyperuricemia and their smoking status, were noted. Hypertension was defined as having a systolic BP >140 mmHg and/or a diastolic BP >90 mmHg or as using antihypertensive medication. Diabetes was defined as having a history of treatment with either insulin or oral hypoglycemic medication, and additional criteria were having a fasting plasma glucose level >126 mg/dl or a casual plasma glucose level >200 mg/dl. We also reviewed the types and distribution of antihypertensive agents in the medical records of each patient.

Patients underwent measurements for baPWV, ABI, BP, heart rate, left ventricular (LV) fractional shortening, and laboratory examinations of venous blood samples before and 3, 6, 12, 24, 36, 48 and 60 months after treatment. In the present study, the doses of fluvastatin and bezafibrate were nearly identical to those used in previous clinical studies.[18–23]

Measurements of PWV The baPWV was measured using a pulse pressure analyzer (Form/ABI, Model BP-203RPE-II; Colin Medical Technology Co Ltd, Komaki, Japan) with simultaneous recordings of bilateral brachial and ankle BP, electrocardiogram and heart sound while the participants were resting in the supine position. A detailed description of the measurements, including validity and reproducibility, is provided elsewhere.[12,13] Heart rate was settled at 60–80 beats/min after at least 5 min rest, 2 measurements were performed on each leg, and the average values, expressed as cm/s, were used in the analysis.

Laboratory Measurements Serum levels of TC, low-

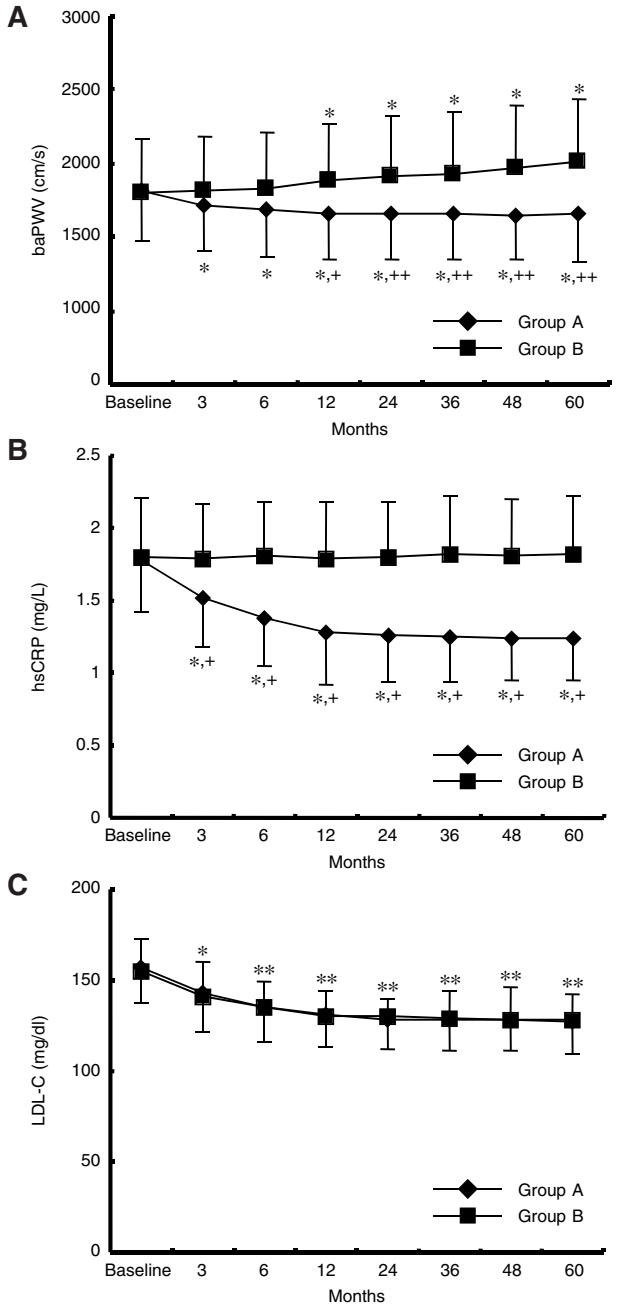

Fig 1. (A) Serial changes in brachial-ankle (ba) pulse wave velocity (PWV) in Protocol 1. In group A, there was a progressive reduction in the baPWV by 12 months after fluvastatin, and improvement was maintained until 5 years after treatment. In group B, the PWV was progressively increased over the follow-up period. Group A, patients receiving 20–40 mg/day of fluvastatin; group B, patients receiving non-statin antihyperlipidemic drug (200–400 mg/day of bezafibrate). *p<0.01 vs baseline, $^{+}$p<0.01 and $^{++}$p<0.001 vs group B. (B) Serial changes in serum high-sensitivity C-reactive protein (hsCRP) level in Protocol 1. In group A, serum hsCRP level was significantly decreased after 3 months of fluvastatin treatment. This improvement was further enhanced for the next 9 months and the variables remained constant thereafter. In group B, there was no change in the serum hsCRP level during the follow-up period. *p<0.001 vs baseline and $^{+}$p<0.001 vs group B. (C) Serial changes in serum low-density lipoprotein-cholesterol (LDL-C) level in Protocol 1. In group A, there was a progressive decrease in the serum LDL-C level by 12 months after fluvastatin treatment, and this was maintained until 5 years after treatment. Patients in group B showed identical changes in their levels of serum LDL-C. *p<0.01 and **p<0.001 vs baseline.

density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), TG, high-sensitivity (hs) CRP, fasting plasma glucose, hemoglobin A_{1c}, and uric acid were measured using standard methods. All blood samples were obtained in the morning after the patient had fasted, on the same day as the baPWV measurements.

Protocol 2

In a subgroup of patients (6 men and 12 women, aged 56–76 years, mean 67.2±9.5 years) who were being treated with 200–400 mg/day of bezafibrate, the patients were switched from the drug to 20–40 mg/day of fluvastatin and followed for 36 months. As in Protocol 1, patients underwent measurements for baPWV and the same laboratory examinations of venous blood samples before and 3, 6, 12, 24, and 36 months after treatment with fluvastatin.

The study protocol was approved by the Medical Ethics Committee of Shinshu University School of Medicine, and all participants gave their written informed consent before enrolment.

Statistical Analysis Data are expressed as the mean ± SD. Any differences within categorical variables, including gender and prevalence of atherosclerotic risk factors and each medication, were examined using chi-square test or Fisher's exact test. The significance of continuous variables, such as systolic and diastolic BP, heart rate, baPWV, ABI, and biochemical data of blood samples, between the groups was analyzed by two-way analysis of variance for repeated measures and Newmann–Keuls' post hoc test.

The differences in baPWV between the groups before treatment was assessed by a general linear model (GLM) multivariate analysis adjusted for mean BP. Differences in the changes for baPWV and serum CRP level between the final examination at 60 months after treatment and the initial examination before treatment were analyzed by a GLM multivariate analysis with post hoc multiple comparison, with Bonferroni's adjustments for the control of covariates that have been reported to affect the PWV and serum CRP level with continuous variables (ie, initial examination values for age, BMI, baPWV, mean BP, heart rate, serum levels of TC, LDL-C, HDL-C, TG and fasting plasma glucose, and changes in the BMI, mean BP, heart rate, serum levels of TC, LDL-C, HDL-C, TG and fasting plasma glucose during the study period) and categorical variables (ie, smoking status at initial examination and status change during the study period). To identify the effects of persistence of each atherosclerotic risk factor, the same GLM analysis was carried out[24,25] All analyses were performed using SPSS (vers. 11.0) for Windows (SPSS, Chicago, IL, USA), and a p-value of <0.05 was considered statistically significant.

Results

All patients completed the study protocol. There were no adverse side-effects or complications due to drug treatment and no serious inflammation occurred during the follow-up period.

Protocol 1

Baseline Patient Characteristics, baPWV, and Biochemical Data There were no significant differences in age, gender distribution, BMI, systolic and diastolic BP, heart rate, LV fractional shortening and numbers of coronary lesions between the 2 groups before treatment (Table 1).

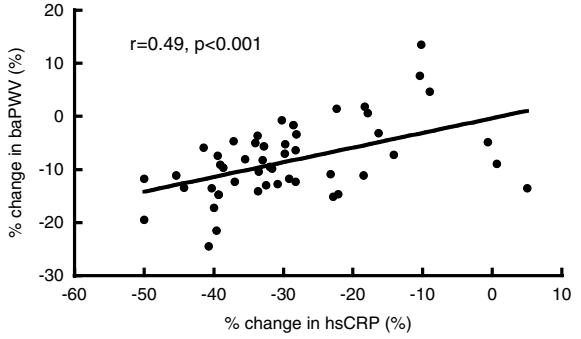

Fig 2. Relationship between brachial-ankle pulse wave velocity (baPWV) and serum high-sensitivity C-reactive protein (hsCRP) level in Protocol 1. In group A, the percentage change in baPWV correlated significantly with that of the serum hsCRP level at 5 years after treatment.

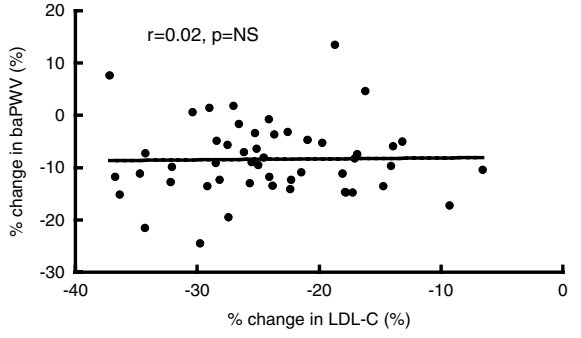

Fig 3. Relationship between brachial-ankle pulse wave velocity (baPWV) and serum low-density lipoprotein-cholesterol (LDL-C) level in Protocol 1. In group A, there was no correlation between the percentage change in baPWV and that of serum LDL-C level at 5 years after treatment.

The prevalence of atherosclerotic risk factors, such as hypertension, diabetes, hyperuricemia and smoking history, the distribution of each antihypertensive drug and the rate of treatment with aspirin were similar between the groups (Table 1). The serum levels of fasting plasma glucose, hemoglobin A_{1c}, TC, LDL-C, HDL-C, TG, baPWV, ABI and hsCRP did not differ between the groups (Table 1).

Serial Changes in baPWV and Biochemical Data In group A, the baPWV and serum levels for CRP and LDL-C were significantly decreased after 3 months of fluvastatin treatment. This improvement was further enhanced for the next 9 months, with the variables remaining constant thereafter (Fig 1). In group B, similarly, the serum LDL-C level was decreased (Fig 1C), but baPWV was significantly increased at 12 months after treatment, with the increase lasting throughout the follow-up period (Fig 1A). There was no change in the serum CRP level (Fig 1B). In group A, at 5 years after treatment, the percentage change in baPWV correlated significantly with that of serum CRP level (r=0.49, p<0.001) (Fig 2), but not with that of serum LDL-C level (r=0.02, p=NS) (Fig 3). There was no relationship between the percentage change in baPWV and that of serum levels of HDL-C or TG. The GLM multivariate analysis demonstrated that elevated BP had a significantly persistent effect on the increase in baPWV, and that an increased level of plasma glucose and the presence of dyslipidemia significantly affected the change in serum CRP level (Table 2).

Table 2 The Results of General Linear Model Multivariate Analysis of Significant Component of Atherosclerotic Risk Factors That Show Persistent Effects on Increase in baPWV and Serum CRP Level

	B (95% CI)	*F value*	*p value*
A. baPWV			
BMI >25 (kg/m²)	*1.2 (–2.5–4.9)*	*0.2*	*NS*
Elevated BP	*4.3 (0.2–8.5)*	*3.7*	*<0.05*
Increased plasma glucose	*1.8 (–2.3–5.9)*	*0.9*	*NS*
Dyslipidemia	*1.6 (–2.8–6.0)*	*0.8*	*NS*
B. CRP level			
BMI >25 (kg/m²)	*1.1 (–2.4–4.6)*	*0.4*	*NS*
Elevated BP	*2.6 (–0.9–6.1)*	*0.9*	*NS*
Increased plasma glucose	*5.3 (2.5–8.1)*	*4.5*	*<0.05*
Dyslipidemia	*5.1 (1.1–9.1)*	*4.3*	*<0.05*

CI, confidence interval. See Table 1 for other abbrevations.

Table 3 Clinical Characteristics in Protocol 2

	Initial	*Final*
Number	*18*	*18*
Age (years)	*67.2±9.5*	
Gender (M/F)	*6/12*	
BMI (kg/m²)	*24.3±5.5*	*24.5±5.7*
Systolic BP (mmHg)	*130±16*	*129±22*
Diastolic BP (mmHg)	*76±15*	*75±18*
Heart rate (beats/min)	*66±10*	*67±13*
LV fractional shortening (%)	*36±6*	*35±7*
Number of CA lesions	*1.8±0.9*	
Risk factors		
Hypertension (%)	*9 (41)*	*10 (45)*
Diabetes (%)	*6 (27)*	*7 (32)*
FPG (mg/dl)	*91±15*	*90±18*
Hemoglobin A_{1c} (%)	*6.2±1.8*	*6.1±1.7*
Serum TC (mg/dl)	*202±35*	*200±35*
Serum LDL-C (mg/dl)	*134±29*	*131±35*
Serum HDL-C (mg/dl)	*42±8*	*41±7*
Serum TG (mg/dl)	*143±17*	*141±15*
Hyperuricemia (%)	*3 (14)*	*4 (18)*
Smoking (%)	*2 (9)*	*2 (9)*
Other drugs		
ACEIs/ARBs (%)	*8 (36)*	*9 (41)*
CCBs (%)	*11 (50)*	*12 (55)*
β-blockers (%)	*2 (9)*	*2 (9)*
α-blockers (%)	*3 (14)*	*3 (14)*
Diuretics (%)	*3 (14)*	*3 (14)*
Aspirin (%)	*16 (73)*	*17 (77)*
baPWV (cm/s)	*1,790±308*	*1,599±327**
ABI	*1.16±0.14*	*1.17±0.16*
Serum hsCRP (mg/L)	*1.75±0.36*	*1.30±0.34**
(range)	*(1.03–3.21)*	*(0.91–1.89)*

**p<0.05 vs initial examination. See Table 1 for abbreviations.*

Protocol 2

The baseline clinical characteristics, baPWV and biochemical data for Protocol 2 are shown in Table 3. Three months after being switched to fluvastatin, patients showed significant improvement in baPWV and serum CRP level despite no significant change in serum LDL-C level (Fig 4). This improvement continued until 12 months after treatment and it was maintained up to 36 months (Fig 4). No significant changes occurred in ABI, BP, heart rate and other clinical findings among each follow-up examination (Table 3).

Discussion

Effects of Fluvastatin on PWV and Biochemical Markers

A number of experimental and clinical studies in the set-

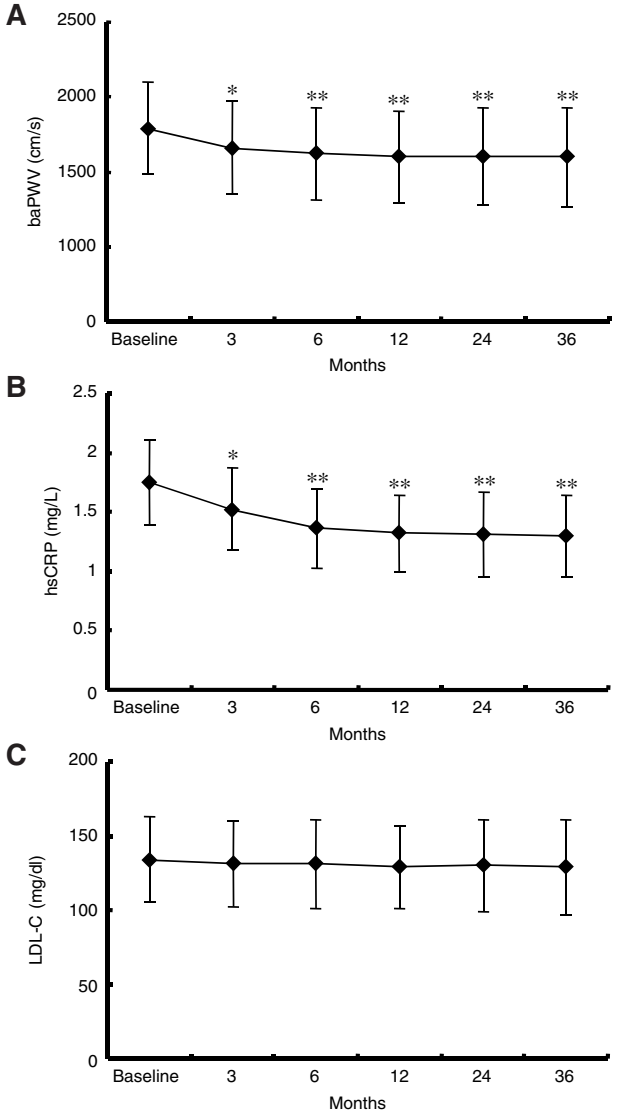

Fig 4. (A) Serial changes in brachial-ankle pulse wave velocity (baPWV) in Protocol 2. Patients who had been switched to fluvastatin showed significant improvement in their baPWV 3 months after the switch. This improvement continued until 12 months after treatment and was maintained up to 36 months. *p<0.01 and **p<0.001 vs baseline. (B) Serial changes in serum high-sensitivity C-reactive protein (hsCRP) level in Protocol 2. Patients showed significant improvement of hsCRP 3 months after the treatment change. This improvement continued until 12 months after treatment and was maintained up to 36 months. *p<0.01 and **p<0.001 vs baseline. (C) Serial changes in serum low-density lipoprotein-cholesterol (LDL-C) level in Protocol 2. There was no significant change in serum LDL-C level over the follow-up period.

ting of hypercholesterolemia have shown improvement of arterial stiffness with cholesterol-lowering therapy, including treatment with statins. In the cholesterol-fed rabbits, pitavastatin exerted anti-atherogenic effects resulting in reduced aortic stiffness via alterations of activities of vascular oxidative stress, Cu/Zn superoxide dismutase, and peroxisome proliferators-activated receptors.[26] In a clinical study by Shige et al, 4 weeks of simvastatin treatment resulted in improvement of peripheral but not central PWV in patients with hypercholesterolemia.[27] In contrast, reduced large artery stiffness was observed after 3 months of atorvastatin treatment in patients with isolated systolic hypertension and normocholesterolemia.[28] Treatment with 40 mg/day of fluvastatin for 12 months improved arterial sclerosis, according to values of integrated backscatter and baPWV, in patients with hyperlipidemia.[22] Recently, Ichihara et al noted that despite the identical lowering of serum CRP level among the 3 statins, 20 mg/day of fluvastatin, but not pravastatin or simvastatin, progressively reduced baPWV in hyperlipidemic hypertensive patients, in parallel with a decrease in serum LDL-C level without changing BP, during the 12 months of treatment.[18] Non-statin antihyperlipidemic drugs, such as clofibrate and probucol, failed to improve these biomechanical and biochemical parameters.[18] Although fluvastatin possesses lipid-independent pleiotropic effects, including anti-atherogenic properties,[29,30] its stronger antioxidative action, when compared with other statins, has been suggested as one of the possible mechanisms for improvement in aortic stiffness.

In the present study, a significant reduction in baPWV was found at 3 months after fluvastatin, which lasted up to 12 months, as well as decreases in serum LDL-C and hsCRP levels in patients with CAD and hyperlipidemia, although we did not assess its dose-dependent effects. In contrast, despite serum lipid levels also being lowered, baPWV was progressively increased and hsCRP remained unchanged, after bezafibrate during the follow-up treatment period. These findings are consistent with those by Ichihara et al.[18] In the present study, we observed that the improvement of baPWV, serum lipids and CRP was maintained until 5 years after treatment with fluvastatin. These beneficial effects were found to be independent of BP. Although we did not measure baPWV shortly after treatment and cannot offer the precise mechanisms for decreased baPWV at 3 months after fluvastatin, its action on several biochemical substances, such as nitric oxide, might cause reduced baPWV rather than an improvement in the remodeling of the vascular wall. It is of great interest that there was a significant correlation between the magnitude of improvement of baPWV and that of CRP after treatment, suggesting that the anti-inflammatory action of fluvastatin might contribute to the favorable effect on arterial stiffness and its maintenance. In addition, we found that persistent elevated BP plays a role in accelerating arterial stiffness, and that increased plasma glucose level and dyslipidemia are important factors affecting serum CRP level. In the present study, a subgroup of patients who had been switched from non-statin antihyperlipidemic agents to fluvastatin showed a significant improvement in baPWV and serum CRP level until 12 months after the switch, and this improvement was maintained up to 36 months. These improvements occurred independent of BP and serum lipid levels.

It is generally recognized that PWV integrates functional and structural elements and can be regarded as an integrated index of vascular function. Many drugs affect PWV and estimates of central waveform morphology derived from arteries and, thus, it would be expected that drug interventions that lower BP would lead to a decrease in PWV. In contrast, drug-induced changes in elastic modulus, wall thickness, and diameter of the arteries resulting from vascular remodeling would be expected to directly influence the PWV independent of BP.[31,32] Although the complete evaluation of the mechanical properties of large arteries is difficult in the clinical setting, the results of the present study demonstrate that treatment with fluvastatin is associated with improvement of baPWV, which might be attributed to favorable vascular structural changes of both the central and

peripheral arteries, as assessed with baPWV, and its beneficial effects persisted for long-term period, independent of BP changes in patients with CAD and hyperlipidemia.

Limitations

There were several limitations to the present study. First, the exact prognostic value of baPWV was unclear because our study was limited to a relatively small number of patients. Second, although the beneficial effects of fluvastatin on arterial stiffness lasted up to 5 years in Protocol 1 and they were maintained up to 3 years in Protocol 2, we have no information on how long the benefits might continue in the clinical setting. Further longer follow-up studies will be required to resolve this issue. A final consideration relates to the method for measuring PWV; that is, the baPWV itself is closely dependent on BP levels during measurement. More recently a new index, the so-called cardio-ankle vascular index (CAVI), which is adjusted for BP and hypothesized to measure arterial stiffness independent of BP, has been developed as an alternative method to assess arterial distensibility[33] and its validity and usefulness have been confirmed[34,35] Prospective studies using techniques measuring CAVI, as well as carotid-femoral PWV, will be necessary to confirm the results of our study.

Conclusion

We assessed the long-term effects of fluvastatin on arterial stiffness, as assessed with baPWV, serum lipids and hsCRP, in patients with CAD and hyperlipidemia. The results demonstrated that the beneficial vascular effects of fluvastatin persisted for a long period in such patients. The anti-inflammatory action of fluvastatin might contribute to the favorable effect on arterial stiffness and its maintenance.

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References

1. Safer ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003; **107:** 2864–2869.
2. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005; **25:** 932–943.
3. Cohn JN. Arterial stiffness, vascular disease, and risk of cardiovascular events. *Circulation* 2006; **113:** 601–603.
4. Hirata K, Kawakami M, O'Rourke MF. Pulse wave analysis and pulse wave velocity: A review of blood pressure interpretation 100 years after Korotkov. *Circ J* 2006; **70:** 1231–1239.
5. Fukuhara M, Matsumura K, Ansai T, Takata Y, Sonoki K, Akifusa S, et al. Prediction of cognitive function by arterial stiffness in the very elderly. *Circ J* 2006; **70:** 756–761.
6. Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Stiffness of capacitative and conduit arteries: Prognostic significance for end-stage renal disease patients. *Hypertension* 2005; **45:** 592–596.
7. Boutouyrie P, Isabelle A, Asmar R, Gatier I, Benetos A, Lacolley P, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: A longitudinal study. *Hypertension* 2002; **39:** 10–15.
8. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: An integrated index of vascular function? *Circulation* 2002; **106:** 2085–2090.
9. Shokawa T, Imazu M, Yamamoto H, Toyofuku M, Tasaki N, Okimoto T, et al. Pulse wave velocity predicts cardiovascular mortality: Findings from the Hawaii–Los Angeles–Hiroshima study. *Circ J* 2005; **69:** 259–264.
10. Mattace-Raso FUS, van der Cammen TJM, Hofman A, van Popele NM, Bos ML, Schalekamp MADH, et al. Arterial stiffness and risk of coronary heart disease and stroke: The Rotterdam Study. *Circulation* 2006; **113:** 657–663.
11. Hansen TW, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, et al. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; **113:** 664–670.
12. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25:** 359–364.
13. Sugawara J, Hayashi K, Yokoi T, Cortez-Cooper MY, DeVan AE, Anton MA, et al. Brachial-ankle pulse wave velocity: An index of central arterial stiffness? *J Hum Hypertens* 2005; **19:** 401–406.
14. Yamashina A, Tomiyama H, Arai T, Hirose KI, Koji Y, Hirayama Y, et al. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens Res* 2003; **26:** 615–622.
15. Munakata M, Ito N, Nunokawa T, Yoshinaga K. Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. *Am J Hypertens* 2003; **16:** 653–657.
16. Imanishi R, Seto S, Toda G, Yoshida M, Ohtsuru A, Koide Y, et al. High brachial-ankle pulse wave velocity is an independent predictor of the presence of coronary artery disease in men. *Hypertens Res* 2004; **27:** 71–78.
17. Tomiyama H, Koji Y, Yambe M, Shiina K, Motobe K, Yamada J, et al. Brachial-ankle pulse wave velocity is a simple and independent predictor of prognosis in patients with acute coronary syndrome. *Circ J* 2005; **69:** 815–822.
18. Ichihara A, Hayashi M, Koura Y, Tada Y, Kaneshiro Y, Saruta T. Long-term effects of statins on arterial pressure and stiffness of hypertensives. *J Hum Hypertens* 2005; **19:** 103–109.
19. März W, Scharnagl H, Ableshauser C, Hoffmann MM, Berg A, Keul J, et al. Fluvastatin lowers atherogenic dense low-density lipoproteins in postmenopausal women with the atherogenic lipoprotein phenotype. *Circulation* 2001; **103:** 1942–1948.
20. Inoue T, Hayashi M, Takayanagi K, Morooka S. Lipid-lowering therapy with fluvastatin inhibits oxidative modification of low density lipoprotein and improves vascular endothelial function in hypercholesterolemic patients. *Atherosclerosis* 2002; **160:** 369–376.
21. Anderssen SA, Hjelstuen AK, Hjermann I, Bjerkan K, Holme I. Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. *Atherosclerosis* 2005; **178:** 387–397.
22. Yokoyama H, Kawasaki M, Ito Y, Minatoguchi S, Fujiwara H. Effects of fluvastatin on the carotid arterial media as assessed by integrated backscatter ultrasound compared with pulse-wave velocity. *J Am Coll Cardiol* 2005; **46:** 2031–2037.
23. Haramaki N, Ikeda H, Takenaka K, Katoh A, Sugano R, Yamagishi SI, et al. Fluvastatin alters platelet aggregability in patients with hypercholesterolemia: Possible improvement of intraplatelet redox imbalance via HMG-CoA reductase. *Arterioscler Thromb Vasc Biol* 2007; **27:** 1471–1477.
24. Tomiyama H, Hashimoto H, Hirayama Y, Yambe M, Yamada J, Koji Y, et al. Synergistic acceleration of arterial stiffening in the presence of raised blood pressure and raised plasma glucose. *Hypertension* 2006; **47:** 180–188.
25. Tomiyama H, Hirayama Y, Hashimoto H, Yambe M, Yamada J, Koji Y, et al. The effects of changes in the metabolic syndrome detection status on arterial stiffening: A prospective study. *Hypertens Res* 2006; **29:** 673–678.
26. Umeji K, Umemoto S, Itoh S, Tanaka M, Kawahara S, Fukai T, et al. Comparative effects of pitavastatin and probucol on oxidative stress, Cu/Zn superoxide dismutase, PPAR-γ, and aortic stiffness in hypercholesterolemia. *Am J Physiol Heart Circ Physiol* 2006; **291:** H2522–H2532.
27. Shige H, Dart A, Nestel P. Simvastatin improves arterial compliance in the lower limb but not in the aorta. *Atherosclerosis* 2001; **155:** 245–250.
28. Ferrier KE, Muhlmann MH, Baguet JP, Cameron JD, Jennings GL, Dart AM, et al. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *J Am Coll Cardiol* 2002; **39:** 1020–1025.
29. Corsini A, Jacobson TA, Ballantyne CM. Fluvastatin: Clinical and safety profile. *Drugs* 2004; **64:** 1305–1323.
30. Liberropoulos EN, Daskalopoulou SS, Mikhailidis DP, Wierzbicki

AS, Elisaf MS. A review of the lipid-related effects of fluvastatin. *Curr Med Res Opin* 2005; **21:** 231–243.
31. Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens* 2005; **18:** 3S–10S.
32. Hope SA, Hughes AD. Drug effects on the mechanical properties of large arteries in humans. *Clin Exp Pharmacol Physiol* 2007; **34:** 688–693.
33. Yambe T, Yoshizawa M, Saijyo Y, Yamaguchi T, Shibata M, Konno S, et al. Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). *Biomed Pharmacother* 2004; **58**(Suppl)**:** S95–S98.
34. Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, et al. Clinical significance and reproducibility of new arterial distensibility index. *Circ J* 2007; **71:** 89–94.
35. Okura T, Watanabe S, Kurata M, Manabe S, Koresawa M, Irita J, et al. Relationship between cardio-ankle vascular index (CAVI) and carotid atherosclerosis in patients with essential hypertension. *Hypertens Res* 2007; **30:** 335–340.