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Combined vascular effects of HMG-CoA reductase inhibitor and angiotensin receptor blocker in non-diabetic patients undergoing peritoneal dialysis

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Abstract

Background. Statins and angiotensin receptor blockers (ARBs) are known to improve vascular dysfunction in patients with chronic kidney disease. However, these effects have been inconsistent in dialysis patients. Moreover, it is currently unknown whether adding statins to ARBs improves vascular dysfunction better than ARB monotherapy in these patients.

Methods. We conducted a prospective open randomized trial to investigate the effects of statin add-on to ARB on vascular protection in 124 nondiabetic patients undergoing peritoneal dialysis (PD). Initially, all patients received 80 mg/day of valsartan for 6 months. Excluding 10 patients who dropped out during this period, patients were randomly assigned to continue ARB treatment alone ($n = 57$) or to receive 10 mg/day of rosuvastatin ($n = 57$) added to ARB for the next 6 months. To assess vascular function, endothelium-dependent vasodilation and arterial stiffness were determined by brachial artery flow-mediated dilation (FMD) and brachial-ankle pulse wave velocity (baPWV), respectively.

Results. Compared to baseline values, ARB treatment for the first 6 months significantly improved FMD% (2.97 ± 2.64 to 3.57 ± 2.58 %, $P < 0.001$). In addition, there was a small but significant decrease in baPWV during this period (1691.5 ± 276.3 to 1635.0 ± 278.6 cm/s, $P = 0.048$). After randomization, add-on treatment further improved FMD% (3.57 ± 2.73 to 4.24 ± 2.77 %, $P = 0.003$), whereas ARB monotherapy did not ($P = 0.02$ for between-group difference). Further slight improvement in baPWV (1617.0 ± 280.9 to 1528.9 ± 266.8 cm/s, $P = 0.021$) was observed only in the combined treatment group ($P = 0.28$ for between-group difference).

Conclusions. Adding a statin to the ARB was of some help in improving vascular dysfunction more effectively than ARB monotherapy in nondiabetic PD patients. However, whether such limited improvements can lead to better clinical outcomes requires further investigation.

Keywords: angiotensin receptor blocker; arterial stiffness; endothelial function; peritoneal dialysis; statin

Introduction

Functional changes in vascular endothelial cells and vascular smooth muscle cells (VSMCs) influence large artery compliance, thus arterial stiffness is strongly affected by endothelial cell signaling and VSMC tone [1]. The changes in arterial distensibility and stiffness in patients with chronic kidney disease (CKD) are different from those in control subjects [2]. Vascular changes are known to develop early during the course of renal insufficiency and progress as kidney function declines. In addition, vascular remodeling occurs in response to increased hemodynamic burden, chronic uremia, inflammation, oxidative stress and extensive vascular calcification caused by CKD progression [3]. Moreover, these vascular abnormalities are reported to be independent predictors of cardiovascular mortality in patients with end-stage renal disease (ESRD) [4–7].

For >10 years, renin–angiotensin system (RAS) blockades and 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors have been widely used to reduce cardiovascular risk based on the results of many large-scale clinical studies [8, 9]. In addition, these drugs are known to reduce inflammation and oxidative stress and to improve vascular dysfunction in the general population as well as in CKD patients prior to dialysis [10, 11]. Different from the general population, however, whether such drugs are beneficial in preventing cardiovascular events is not clear in patients with CKD [12–14]. Although RAS blockades not only delay the progression of kidney disease but also decrease all-cause mortality in patients with CKD prior to dialysis, their effect on cardiovascular mortality was not satisfactory in this population [15, 16]. In addition, in patients

undergoing hemodialysis, statin therapy failed to decrease all-cause mortality [14] and cardiovascular events [17]. Nevertheless, RAS blockades and statins still constitute the main therapeutic options for the treatment and prevention of cardiovascular disease (CVD) in ESRD patients.

The morality rates of diabetic ESRD patients are significantly higher than those of nondiabetic patients, mainly because of preexisting severely compromised cardiovascular conditions [18]. Because diabetes is largely responsible for the generation of oxidative stress and inflammation, which are major culprits in vascular pathology [19], nondiabetic ESRD patients are presumed to have different vascular characteristics compared with those with diabetes on dialysis despite the development and progression of vascular dysfunction caused by uremia *per se* [2]. In this regard, a fortifying strategy for vascular protection is necessary to improve patient outcomes particularly in nondiabetic ESRD patients, but this has been largely unexplored. In addition, there have been few studies on the effects of RAS blockades and statins on vascular function in these patients. Therefore, we undertook this study to investigate whether adding a statin to an angiotensin II type 1 receptor blocker (ARB) may confer greater vascular protection than ARB monotherapy in nondiabetic patients undergoing long-term peritoneal dialysis (PD).

Subjects and methods

Study subjects

Between January 2008 and December 2008, 300 patients who were over 20 years of age and had been maintained on PD >3 months were screened for this study. Because we were mainly concerned about the effects of combined treatment of ARB and statin on vascular function in ESRD patients with low-risk profiles for CVD, patients were considered eligible if they had no diabetes and no previous history of cardiovascular comorbidities. In addition, we excluded patients with overt infection during the last 3 months prior to the study and a history of malignancy or other chronic inflammatory disease, such as systemic lupus erythematosus or rheumatoid arthritis. Among the screened patients, 124 patients who met the criteria and gave informed consent were enrolled in this study (Figure 1). The study was approved by the institutional review board for human research at our center (2008–06).

Study design

We conducted a prospective, randomized, open-label trial. This study had an open two-phase design. After a 4-week washout period, all patients (n = 124) were treated with a single ARB, 80 mg/day of valsartan for 6 months prior to randomization because functional antagonistic effects of various ARBs are different [20, 21] and it takes several months for the full effect of RAS inhibition to show up. Excluding 10 patients who dropped out during this first 6-month period, patients then were randomly assigned to continue ARB monotherapy (n = 57) or to receive add-on treatment with 10 mg/day of rosuvastatin (n = 57) in addition to ARB for the next 6 months. Randomization was performed by a 1:1 ratio using computer-generated random numbers.

Data collection

Demographic and clinical data were recorded in the beginning of the study: age, gender, body mass index (BMI) calculated as weight/(height)^2, primary renal disease, previous history of CVD and duration of dialysis. CVD was defined as a history of coronary, cerebrovascular or peripheral vascular disease. Following laboratory data were measured from blood samples: hemoglobin, blood urea nitrogen, creatinine, albumin, calcium, phosphorus, intact parathyroid hormone, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol and triglyceride. Kt/V urea was determined from the total loss of urea nitrogen in the spent dialysate using the Watson equation [22].

Flow-mediated dilation and nitroglycerin-mediated dilation

Endothelium-dependent vasodilation was assessed noninvasively by determining flow-mediated dilation (FMD) using high-resolution ultrasound (Logiq 7; GE Medical Systems, Milwaukee, WI). Patients were informed to fast overnight, not to exercise, not to ingest substances that might affect FMD, such as caffeine, high-fat foods or vitamin C, and not to

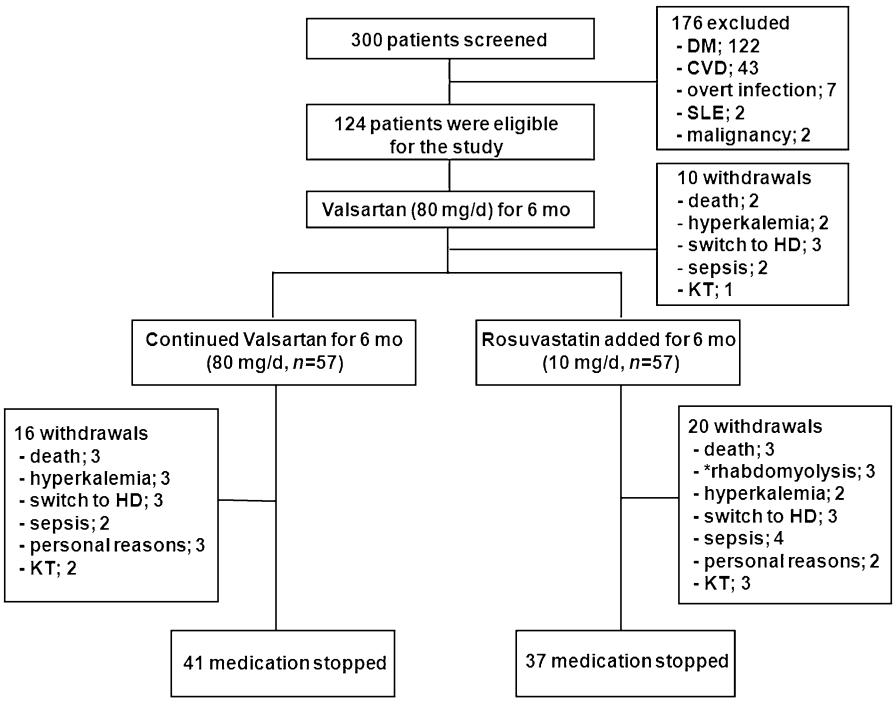

Fig. 1. Flow of the study subjects through each stage of the study. DM, diabetes mellitus; SLE, systemic lupus erythematosus; HD, hemodialysis; KT, kidney transplantation. *Rhabdomyolysis is defined as creatine kinase elevation less than five times the upper limit of normal (reference range 44 ~ 245 IU/L).

smoke for at least 12 h before the study. The measurement protocol for brachial artery (BA) FMD has also been described in detail elsewhere [23]. The BA-FMD and nitroglycerin-mediated dilation (NMD) were calculated as the percentage increases in the BA diameter relative to the mean baseline diameter during reactive hyperemia and after administration of nitroglycerine, respectively. All ultrasound measurements were performed by a single observer who was blinded to patient information and treatment allocation. Intraobserver within-subjects coefficient of variations for BA-FMD and NMD were 5.5 ± 0.7 and 7.7 ± 1.3%, respectively.

Brachial-ankle pulse wave velocity

The baPWV was measured as described previously [24]. Electrocardiogram, bilateral brachial and ankle blood pressures (BP), and brachial and post-tibial arterial pulse waves were simultaneously measured with avascular testing device (VP-2000 PWV®; Nippon Colin Ltd, Komaki, Japan). Bilateral brachial and post-tibial arterial pressure waveforms were stored for 10 s by extremities cuffs connected to a plethysmographic sensor and an oscillometric pressure sensor wrapped on both arms and ankles. The baPWV was calculated from the distance between two arterial recording sites divided by transit time.

Assessment of volume status

Volume status was estimated by a multifrequency bioelectrical impedance analysis (BIA) device (X-scan body composition analyzer; Jawon Medical, Kyungsan, Korea) with tetrapolar electrodes. BIA was performed between both hands and ankles in an upright position. Both hands were held at a 45° angle away from the body. X-scan uses 1, 5, 50, 250, 550 and 1000 kHz frequencies to analyze intracellular fluid, extracellular fluid (ECF) and total body water (TBW). ECF was normalized to height and TBW. The intra-examination coefficient of variation for BIA was 2.2%.

Measurement of serum inflammatory markers and oxidative stress

High-sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6) were determined using a latex-enhanced immunonephelometric method on a BN II analyzer (Dade Behring, Newark, DE) and a commercially available enzyme-linked immunoabsorbent assay (ELISA) kit (R&D Systems Europe, Oxon, UK), respectively. Fibrinogen was measured in citrated plasma by a modified clot-rate assay using a Pacific Hemostasis Assay Set (Humlersville, NC). In addition, the concentration of 8-isoprostane, a maker for oxidative stress, was measured by enzyme immunoassay (Cayman Chemical, Ann Arbor, MI).

Power calculation

The number of patients needed to detect a 10% difference of brachial-ankle pulse wave velocity (baPWV) between the two groups over 6 months with two longitudinal measurements with a power of 90%, an α value of 0.05, and a standard deviation of 240 was 47 patients per group. Considering a dropout percentage of 20%, 59 patients were needed for each group.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0 (SPSS, Inc., Chicago, IL). Data were expressed as mean ± SD or median with range for the skewed data. In graphs, however, data were expressed as mean ± SEM. The Kolmogorov–Smirnov test was used to analyze the normality of the distribution of parameters. Comparisons between the two groups were made by the chi-square test and Student's *t*-test for normally distributed variables. Paired *t*-test was used to determine the differences in the measured parameters between the two periods. For skewed variables, the Mann–Whitney *U*-test and Wilcoxon signed-rank test were conducted. In addition, differences in FMD, NMD and baPWV were further compared between statin add-on treatment group and ARB monotherapy group using mixed-effects models. Post-treatment results were presented as an estimate of the mean difference and 95% confidence interval (CI). A value of $P < 0.05$ was considered significant. All analyses were performed on an intention-to-treat basis.

Results

Demographic and clinical data

Table 1 details the baseline characteristics of the 124 patients. The mean age was 48.8 years, and 44.4% were male. The mean duration of dialysis was 76.7 months and the mean BMI was 22.8 kg/m^2. There were 83 anuric patients. Baseline laboratory data are presented in Table 2.

Effects of 6-month ARB treatment on vascular function

Compared with the baseline values, 6-month ARB treatment significantly improved FMD (2.97 ± 2.64 to 3.57 ± 2.58 %, $P < 0.001$) but not NMD. There was a small but significant decrease in baPWV (1691.5 ± 276.3

Table 1. Patient characteristics[a]

Number of patients	124
Age (years)	48.8 ± 11.0
Gender (male:female)	55:69
BMI (kg/m^2)	22.8 ± 3.0
PD duration (months)	76.7 ± 50.6
Biocompatible PD solution, *n* (%)	114 (92.3)
Primary disease, *n* (%)	
Chronic glomerulonephritis	62 (50.0)
Hypertension	32 (25.6)
Polycystic kidney disease	3 (2.6)
Others	6 (5.1)
Unknown	21 (16.7)
Antihypertensive medications, *n* (%)	
ACE inhibitors/ARBs	89 (71.8)
Beta blockers	69 (55.6)
Calcium channel blockers	82 (65.9)
Others	64 (51.5)
Active vitamin D treatment	41 (33.3)

[a]All data were expressed as mean ± SD. ACE, angiotensin-converting enzyme.

Table 2. Changes of clinical and laboratory parameters during 6-months ARB treatment[a]

	Baseline	6 Months
SBP (mmHg)	133.3 ± 19.6	133.4 ± 20.4
DBP (mmHg)	80.8 ± 9.7	80.6 ± 11.0
Haemoglobin (g/dL)	10.9 ± 1.7	10.9 ± 1.6
Calcium (mg/dL)	8.8 ± 0.6	8.9 ± 0.8
Phosphorus (mg/dL)	5.0 ± 1.3	5.2 ± 1.1
PTH (pg/mL)	295.8 ± 134.9	264.1 ± 109.1
Serum albumin (g/dL)	3.8 ± 0.4	3.7 ± 0.4
Total cholesterol (mg/dL)	186.9 ± 36.6	184.0 ± 40.0
Triglyceride (mg/dL)	106.5 (35.0–742.0)	95.0 (30.0–932.0)
HDL (mg/dL)	53.1 ± 15.9	49.3 ± 15.0
LDL (mg/dL)	115.4 ± 32.8	115.5 ± 31.5
Fasting glucose (mg/dL)	92.6 ± 18.9	90.5 ± 11.4
Serum fibrinogen (mg/dL)	488.0 ± 91.1	467.4 ± 105.5*
hs-CRP (mg/L)	1.98 ± 1.42	1.53 ± 1.11†
IL-6 (pg/mL)	7.42 ± 2.81	7.00 ± 5.56
8-Isoprostane (pg/mL)	335.0 (50.5–1986.9)	297.7 (16.9–1506.5)
Kt/V	2.14 ± 0.38	2.12 ± 0.44
Total UF volume (mL/day)	1080.5 ± 490.3	1005.2 ± 592.4
Urine volume (mL/day)	440.4 ± 755.0	410.4 ± 664.0
TBW (L)	35.1 ± 6.7	35.0 ± 6.6
ECF (L)	12.9 ± 2.5	12.8 ± 2.4
ECF/height (L/m^2)	8.0 ± 1.3	7.9 ± 1.3
ECF/TBW	0.37 ± 0.01	0.37 ± 0.01

[a]All data are expressed as mean ± SD or median with range for skewed data. SBP, systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone; HDL, high-density lipoprotein, LDL; low-density lipoprotein, hs-CRP; high-sensitivity C-reactive protein, IL-6; interleukin-6, UF, ultrafiltration, TBW, total body water; ECW, extracellular water. *$P < 0.05$ versus baseline, †$P < 0.001$ versus baseline.

to 1635.0 ± 278.6 cm/s, P = 0.048) by ARB treatment (Figure 2). In addition, hs-CRP (1.98 ± 1.42 to 1.53 ± 1.11 mg/L, P < 0.001) and fibrinogen levels (488.0 ± 91.1 to 467.4 ± 105.5 mg/dL, P = 0.028) were significantly decreased after 6-month ARB treatment. IL-6 and 8-isoprostane levels also tended to decrease during the first 6-month ARB treatment but did not reach statistical significance (Table 2).

Effects of add-on treatment with statin to ARB on vascular function

There were no significant differences in age, gender, BP and lipid profiles between the ARB monotherapy and combined groups (Tables 3 and 4). In addition, hs-CRP, IL-6, fibrinogen and 8-isoprostane levels were comparable at the time of randomization (Table 4).

Compared to the vascular function at 6 months, add-on treatment further increased FMD by 18.7% (3.57 ± 2.73 to 4.24 ± 2.77 %, P = 0.003), whereas ARB monotherapy did not (Figure 2). In addition, add-on treatment but not ARB monotherapy resulted in a slight but significant decrease in baPWV by 5.5% (1617.0 ± 280.9 to 1528.9 ± 266.8 cm/s, P = 0.021). During this period, there was no significant alteration in NMD in both treatment groups. In the meantime, statin add-on treatment significantly decreased total cholesterol (182.7 ± 33.4 to 135.7 ± 26.4 mg/dL, P < 0.001) and LDL cholesterol levels (110.8 ± 29.6 to 65.6 ± 21.2 mg/dL, P < 0.001). In addition, serum hs-CRP (1.63 ± 1.10 to 1.24 ± 0.87 mg/L, P = 0.003), IL-6 (7.16 ± 5.65 to 6.40 ± 4.29 pg/mL, P = 0.057) and 8-isoprostane levels [317.5 (18.9–1506.5) to 193.2 (36.9–542.1) ng/mL, P = 0.07] were further decreased by the combined treatment (Table 4).

We calculated the differences in FMD, baPWV, hs-CRP, IL-6 and 8-isoprostane levels during this period and compared these values between the two groups (Figure 3). Compared to ARB monotherapy, the between-group differences in FMD% [0.66 (95% CI, 0.32–1.01) versus 0.10 (−0.23 to 0.45), P = 0.02] and hs-CRP levels [−0.39 (95% CI, −0.61 to −0.17) versus −0.02 (−0.23 to 0.19) mg/L, P = 0.02] were greater in the add-on treatment group. The between-group differences in baPWV (P = 0.28), IL-6 (P = 0.55) and 8-isoprostane (P = 0.65) levels were also greater in the combined treatment group but did not reach statistical significance.

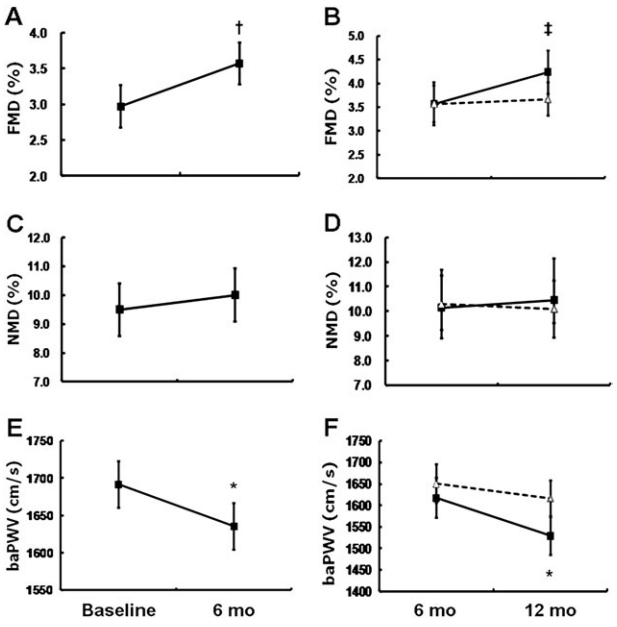

Fig. 2. (**A**, **C** and **E**) Changes of vascular function during 6-month ARB treatment. Compared with the baseline, 6-month ARB treatment significantly improved FMD and decreased baPWV. (**B**, **D** and **F**) Changes of vascular function between the combined therapy and ARB monotherapy group. Compared with the levels at 6 months, add-on treatment with statin (solid line) further improved FMD and decreased baPWV by 15.6 and 5.4%, respectively, whereas valsartan alone did not (dashed line). *P < 0.05 versus baseline, †P < 0.01 versus baseline, ‡P < 0.01 versus baseline. Error bars indicate SE.

Table 3. Comparison of demographic and clinical data at randomization between patients treated with ARB alone and those with combination of ARB and statin[a]

	ARB alone	ARB + statin
Number of patients	57	57
Age (years)	48.8 ± 10.6	48.9 ± 11.5
Gender, male (%)	29 (51.2)	26 (45.9)
BMI (kg/m^2)	22.8 ± 3.2	23.0 ± 2.9
PD duration (months)	77.6 ± 49.0	75.7 ± 52.9
Biocompatible PD solution, *n* (%)	54 (95.1)	51 (89.2)
Antihypertensive medications, *n* (%)		
Beta blockers	47 (82.1)	42 (73.0)
Calcium channel blockers	49 (85.3)	49 (86.4)
Others	36 (63.4)	34 (59.5)
Active vitamin D treatment	21 (36.6)	17 (29.7)

Discussion

Whether statins should be combined with ARBs to boost vascular protection in CKD patients is controversial. Unfortunately, two recent, randomized, controlled, prospective studies showed that statin therapy did not decrease all-cause mortality [14] and cardiovascular events [17] in patients undergoing hemodialysis, suggesting that the pathogenesis of vascular events in ESRD patients may be different from those without ESRD and that earlier statin therapy prior to initiating dialysis may be of benefit. Relevant to this assumption are the results from the Anti-Oxidant Therapy in Chronic Renal Insufficiency (ATIC) study demonstrating that sequential antioxidant treatment with statin, vitamin E and folic acid significantly improved FMD in nondiabetic patients with mild-to-moderate CKD without manifest CVD [11]. On the other hand, to date, there have been only two studies in which ARB treatment significantly improved arterial stiffness in patients on dialysis [10, 25]. Interestingly, patients with diabetes and a history of CVD were excluded in one study [10], and only a small number of patients with diabetes was included in the other [25]. With such a background in mind, in this study, we hypothesized that vascular response to statins and ARBs might be different between diabetic and non-diabetic patients and between patients with and without

Table 4. Changes of clinical and laboratory parameters after randomization[a]

	ARB alone		ARB + statin	
	6 Months	12 Months	6 Months	12 Months
SBP (mmHg)	132.3 ± 20.5	132.6 ± 17.1	134.6 ± 20.5	132.0 ± 16.6
DBP (mmHg)	80.2 ± 10.3	80.0 ± 10.9	80.9 ± 11.9	78.9 ± 8.0
Hemoglobin (g/dL)	11.2 ± 1.5	10.8 ± 1.2	10.6± 1.6	10.4 ± 1.4
Calcium (mg/dL)	8.8 ± 0.8	8.7 ± 0.9	9.0 ± 0.9	8.9 ± 1.0
Phosphorus (mg/dL)	5.1 ± 1.0	5.1 ± 1.3	5.2 ± 1.1	5.0 ± 1.0
PTH (pg/mL)	293.5 ± 184.2	252.4±190.4	231.5 ± 95.6	232.0 ± 89.5
Serum albumin (g/dL)	3.8 ± 0.4	3.8 ± 0.4	3.7 ± 0.4	3.8 ± 0.5
Total cholesterol (mg/dL)	185.2 ± 46.1	197.6 ± 48.1	182.7 ± 33.4	135.7 ± 26.4†
Triglyceride (mg/dL)	97.0 (35.0–932.0)	113.0 (45.0–976.0)	94.0 (30.0–564.0)	86.0* (23.0–454.0)
HDL (mg/dL)	50.7 ± 16.5	48.3 ± 16.4	47.8 ± 13.2	49.7 ± 14.8
LDL (mg/dL)	120.2 ± 32.8	121.4 ± 37.4	110.8 ± 29.6	65.6 ± 21.2†
Fasting glucose (mg/dL)	90.5 ± 13.0	89.8 ± 17.5	90.6 ± 9.4	87.8 ± 9.1
Serum fibrinogen (mg/dL)	467.7 ± 98.5	430.6 ± 75.7*	467.0 ± 114.0	417.9 ± 64.1‡
hs-CRP (mg/L)	1.43 ± 1.14	1.41 ± 1.10	1.63 ± 1.10	1.24 ± 0.87‡
IL-6 (pg/mL)	6.87 ± 5.54	6.67 ± 5.25	7.12 ± 5.65	6.40 ± 4.29
8-isoprostane (pg/mL)	277.1 (16.9–1270.7)	265.9 (61.8–3816.3)	318.0 (18.9–1506.5)	193.2 (36.9–542.1)
Kt/V	2.11 ± 0.47	2.09 ± 0.50	2.13 ± 0.41	2.11 ± 0.44
Total UF volume (mL/day)	1035.1 ± 550.3	1030.8 ± 488.7	982.2 ± 421.4	1015.1 ± 445.8
Urine volume (mL/day)	405.9 ± 612.6	375.9 ± 609.5	428.6 ± 721.2	395.2 ± 557.3
TBW (L)	35.5 ± 6.3	35.8 ± 7.0	34.9 ± 7.1	34.8 ± 6.8
ECF (L)	13.0 ± 2.3	13.2 ± 2.6	12.8 ± 2.6	12.9 ± 2.5
ECF/height (L/m^2)	8.0 ± 1.2	8.1 ± 1.4	7.9 ± 1.4	8.0 ± 1.4
ECF/TBW	0.36 ± 0.04	0.37 ± 0.05	0.37 ± 0.01	0.37 ± 0.01

[a]SBP, systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone; UF, ultra filtration.
*P < 0.05 versus 6 months, †P < 0.01 versus 6 months, ‡P < 0.001.

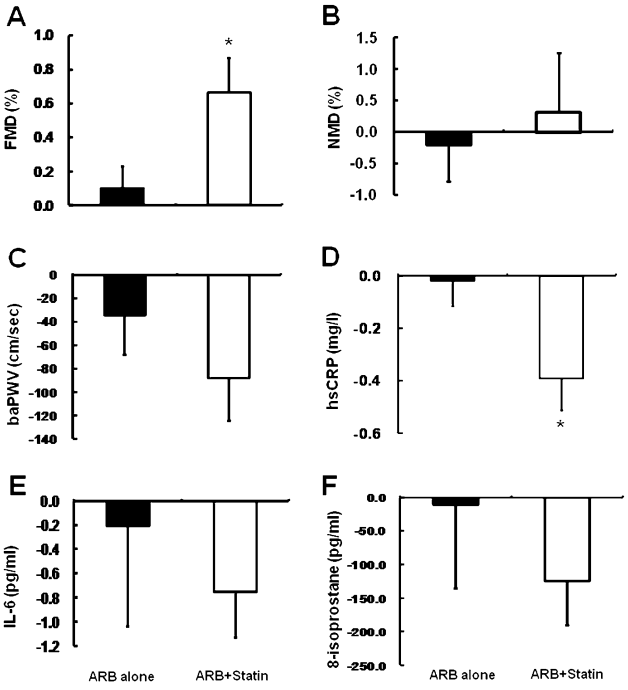

Fig. 3. Between-group differences between ARB monotherapy group and combination therapy group (closed squares ARB monotherapy, open squares ARB + statin). The differences in FMD and hs-CRP were bigger in the combined treatment group than in ARB monotherapy group. *P < 0.05 versus ARB monotherapy. Error bars indicate SE.

evident CVD. Thus, we excluded patients with diabetes and a history of CVD. In addition, the patients in the present study were characterized by young age, normal range of BMI and relatively well-controlled BP. Moreover, only 6.4% of our patients had LDL cholesterol levels over 160 mg/dL and 7.6% had triglyceride levels over 250 mg/dL. These findings indicate that our patients were at a relatively low risk of CVD. To investigate whether add-on treatment with statin to ARB may confer a greater vascular protection in such patients, we conducted a comprehensive assessment of vascular function, including endothelial-dependent vasodilation and arterial stiffness. As a result, we found that compared to ARB monotherapy, add-on treatment further improved endothelial dysfunction. In addition, arterial stiffness was slightly but significantly improved by adding a statin to an ARB, suggesting that combined treatment with a statin and ARB may be of some help in improving vascular dysfunction in these patients.

In this study, we further investigated on parameters associated with vascular function. During the first 6-month ARB treatment, hs-CRP levels were significantly decreased by 23% from baseline. Adding a statin to an ARB further decreased hs-CRP levels by 24%, whereas ARB monotherapy alone did not. Other markers such as fibrinogen, IL-6 and 8-isoprostane showed similar trends but the decreases were more prominent in the combined treatment group. These findings can explain the possible mechanism responsible for the partial improvement in vascular dysfunction in our study. A number of studies have stressed the importance of inflammation and oxidative stress in the development of atherosclerosis and arteriosclerosis [26]. In line with these studies, our study showed improved vascular function along with the decreased levels of the abovementioned markers. Therefore, it can be presumed that systemic inflammation and oxidative stress play an important role in the

development of vascular dysfunction and correction of these detrimental factors is required to recuperate vascular function.

Even though both statin and ARB improved vascular dysfunction in our patients, the degrees of improvement of endothelial dysfunction and arterial stiffness in these patients were relatively smaller than those without CKD in the previous studies [27, 28]. In general, the tunica intima of the arterial wall is made up of one layer of endothelial cells, and the tunica media is composed of VSMC that are surrounded by collagen and elastic fibers [1]. In addition, it is well known that endothelium-derived nitric oxide (NO) is a major physiological regulator of vascular tone and functional and structural changes in vascular endothelial cells and VSMCs influence large artery compliance [1]. Meanwhile, in patients with ESRD, oxidative stress and inflammation are increased in the systemic circulation and are major culprits of decreased NO bioavailability [29]. These patients are also characterized by extensive vascular calcification in the intima, media and elastic fibers of the arterial wall [3]. Therefore, such alterations in the vessels can lead to endothelial and smooth muscle dysfunction, eventually leading to increased arterial stiffness. To date, however, neither statins nor ARBs have been proven to attenuate the rate of progressive vascular calcification [30, 31]. Taken together, it can be surmised that statins and ARBs can improve endothelial dysfunction by decreasing oxidative stress and inflammation in an altered vascular milieu but are of limited help in improving global arterial function because of considerable calcific burden in VSMCs and the surrounding elastic fibers in ESRD patients. These can partly explain attenuated vascular response to these drugs in our study.

Alternatively, such limited vascular response to ARB and/or statin may be attributed to the unique patient characteristics in this study. Most patients had been on long-term PD with a mean duration of 76.7 months. As the ATIC study suggested, the vascular response to such therapy could be different if patients were treated in earlier stages of CKD [11]. In addition, all patients in this study were nondiabetics. Whether statins are as effective in diabetic patients as they are in nondiabetic patients is still under debate. However, the Cholesterol Treatment Trialists' Collaborators suggested that statins were equally effective in reducing vascular events among patients with or without diabetes [32]. Further studies will be necessary to clarify whether statins would still remain effectual in the ESRD population.

It has been reported that vascular function can be considerably affected by diverse factors, such as volume status [33], residual renal function [34] and hypertension [35]. To address this issue, volume status and residual urine volume were monitored during the follow-up period and were found to be unchanged and comparable between the two groups. In addition, patients maintained BP at stable levels during the study period. During the washout period, other antihypertensive medications were prescribed to control BP, thus no significant changes in BP were observed during the follow-up. Therefore, the improvement of vascular function in this study was unlikely to be attributed to the influence of these factors.

Several shortcomings should be discussed in this study. First, this study is limited by the small number of patients and high dropout rates. As described in the Subjects and Methods section, the sample size was calculated before the start of the study. We assumed that a total of 118 subjects would be required to detect 10% difference of baPWV with a dropout percentage of 20% taken into account. However, at the end of study, the actual difference in baPWV between the two groups was $<10\%$ and the dropout rate exceeded 20%. This may explain a lack of statistical power for the between-group difference of baPWV in this study despite a significant decrease in baPWV during 6–12 months only in the combined treatment group. Further studies with a larger sample size or a cross-over design would overcome this limitation. Second, we did not evaluate dose-dependent changes in FMD or baPWV. In the present study, since serum lipid levels in our patients were not so high, 10 mg of rosuvastatin was selected. Whether vascular dysfunction could be further improved by escalating the dose of statin is currently unknown. However, such effects can be expected because there is some evidence that inflammation is more ameliorated by a high dose of statin [36]. Third, this study included only nondiabetic PD patients who did not have cardiovascular cormobidities and were considered to have low cardiovascular risk. Because diabetes is the most common cause of ESRD and CVD is prevalent in ESRD patients [37], it needs to be verified whether our data with such a specific patient cohort can be generalized to other populations. Finally, more detailed information is needed to explain the weak vascular response to statins and ARBs. We evaluated the effects of these drugs on vascular function with respect to decreasing inflammation and oxidative stress, which are well-known strengths of these drugs. However, as aforementioned, the drugs failed to inhibit the progression of vascular calcification. Therefore, further studies on therapeutic strategies for attenuating vascular calcification would be helpful to delineate the relationship between complex vascular pathophysiology and arterial compliance in ESRD patients.

In conclusion, this study demonstrated that combined treatment with a statin and an ARB was more effective in improving endothelial dysfunction compared with ARB monotherapy in nondiabetic PD patients. However, there was only a slight improvement in arterial stiffness by add-on treatment with statins. Therefore, whether such limited improvements in vascular dysfunction can lead to better clinical outcomes needs to be further investigated.

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Conflict of interest statement. None declared.

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