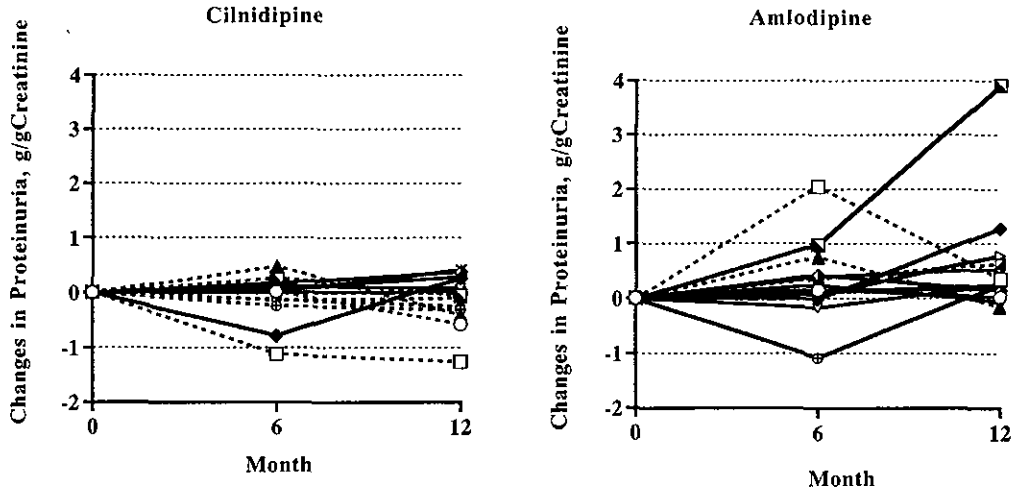

Fig. 1. *Changes in proteinuria in each patient from the baseline level over 12 months. Left column, changes in the cilnidipine group; right column, changes in the amlodipine group.*

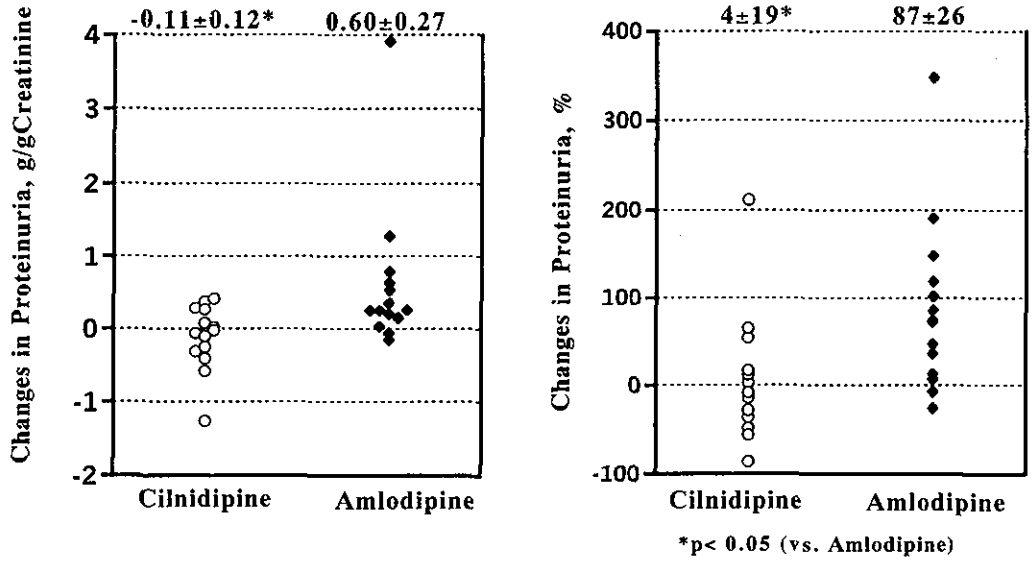

Fig. 2. *Changes in proteinuria at 12 months compared to the baseline levels. Left column, changes in mg/g creatinine; right column, percent changes. The amlodipine group showed significantly higher levels than the cilnidipine group (p<0.05).*

(43%) and chronic glomerulonephritis in 8 patients (57%), and those in the amlodipine group were diabetes mellitus in 10 patients (71%) and chronic glomerulonephritis in 4 patients (29%). There was no significant deviation in any background factor, such as age, gender, or serum Cr (Table 1).

During the trial, no significant changes were observed in systolic or diastolic blood pressure. In addition, no significant differences in systolic or diastolic blood pressure were noted between the two groups. The mean blood pressure remained in the 96–99 mmHg range throughout the follow-up period, and showed no significant difference between the two groups. Heart rate tended to be slower in the cilnidipine group, and the decrease from the baseline value was significant ($p<0.05$) at 6 months after randomization (Table 2).

The mean urinary excretion of protein in a casual urine specimen during the observation period was 0.86±0.16 g/g Cr on the first occasion, and 0.93±0.15 g/g Cr on the second occasion, with no significant difference. There was a good correlation between the measurements on the first and second occasions ($r=0.93$, $p<0.0001$), suggesting that the evaluation of proteinuria standardized for Cr is appropriate. An increase in proteinuria was noted in the amlodipine group, but not in the cilnidipine group (Table 2, Fig. 1). The amlodipine group showed a significantly ($p<0.05$) higher level and rate of change in proteinuria 12 months after randomization (Fig. 2). When analysis was restricted to those patients

Table 3. Logistic Regression Analysis for the Changes in Proteinuria

Variable	Partial correlation coefficient	χ^2 value	p
Baseline serum Cr	0.127	2.589	0.108
Changes in SBP	0.000	0.379	0.538
Changes in DBP	0.000	0.002	0.966
Class of CCB (amlodipine or cilnidipine)	0.249	4.266	0.039
Cause of renal diseases (diabetes or glomerulonephritis)	0.000	0.011	0.916
ACEI or ARB (with or without)	0.000	0.138	0.711

Cr, creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

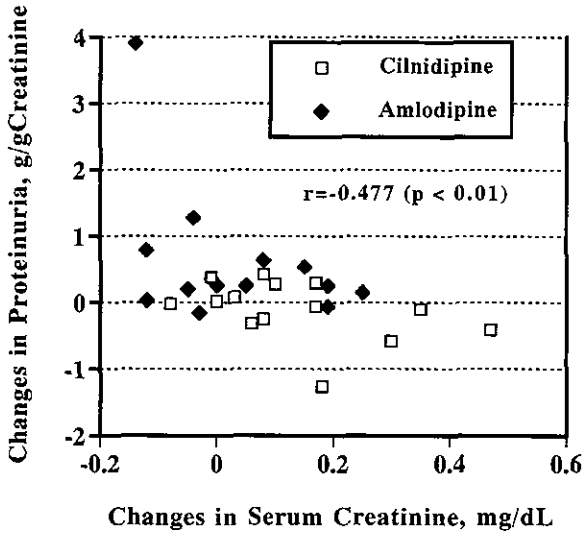

Fig. 3. *Correlation between changes in serum creatinine (Cr) levels and changes in proteinuria. A significant inverse correlation was observed* (r=−*0.477*, p<*0.01*). *The values for the cilnidipine group are distributed in the lower right area, and those for the amlodipine group in the upper left region.*

who were given amlodipine before randomization, the same changes in proteinuria were observed (cilnidipine *vs.* amlodipine, −0.05±0.11 g/g Cr *vs.*+0.29±0.10, $p<0.05$). The urinary excretion of albumin tended to increase in the amlodipine group in comparison with the cilnidipine group ($p<0.1$, Table 2). Analysis of the rate of change in proteinuria in each patient after 12 months showed a more than 25% decrease in proteinuria in 6 (43%) of the 14 patients in the cilnidipine group. In contrast, a more than 50% increase in proteinuria was observed in 7 patients (50%) in the amlodipine group. As shown by logistic regression analysis in Table 3, only the CCB class was a significant variable for predicting the changes in proteinuria. The cause of renal diseases or the combined use of RA inhibitors did not influence the effects of CCBs on urinary protein excretion.

Follow-up of renal function showed a significant increase in serum Cr in the cilnidipine group (Table 2). Serum β_2-microglobulin also tended to increase in the cilnidipine group, but not significantly in comparison with the amlodipine group (Table 2). As shown in Fig. 3, an inverse correlation existed between the increase in serum Cr and that in the urinary excretion of protein ($r=-0.477$, $p<0.01$).

Discussion

The results of this study suggest that the effects of dihydropyridine CCBs on proteinuria and renal function vary with the channel blocker class. In contrast to amlodipine, the 12-month administration of cilnidipine, an N-type CCB, in combination with other antihypertensive drugs suppressed the increase in proteinuria, and mildly reduced the glomerular filtration rate. When the effects of cilnidipine and amlodipine were combined, a significant inverse relationship was observed in the changes between proteinuria and serum creatinine (Fig. 3). These effects of cilnidipine on proteinuria and renal function resembled those of RA inhibitors.

The kidney is densely innervated by the renal sympathetic nerves. The renal sympathetic nerves run together with the renal artery, enter the kidney at the renal hilum, and supplies the interlobar arteries, arcuate arteries, afferent arterioles, and efferent arterioles. Sympathetic innervation of the renal tubules has also been reported (*17*). The uptake of tritium-labeled norepinephrine has been shown to be most intense in the afferent arterioles, followed by the efferent arterioles, interlobular arteries, cortical capillaries, and arcuate arteries (*18*). In another study, an L-type CCB, nifedipine, failed to suppress the norepinephrine release by electric stimulation of the renal nerve, whereas cilnidipine suppressed its release (*19*), indicating that unlike nifedipine, cilnidipine has N-type calcium channel antagonistic action.

L-type calcium channels are distributed mainly in the smooth muscle cells of afferent arterioles, but not of efferent arterioles (*20*). It is well known that almost all dihydropyridine CCBs, including cilnidipine and amlodipine, have the ability to block L-type calcium channels, leading to dilatation of the afferent arterioles. In addition, an analysis of the effects of CCBs on glomerular hemodynamics showed that cilnidipine dilated both afferent and efferent arterioles to a similar extent, whereas nifedipine selectively dilated afferent

arterioles (*21*). Dilatation of efferent arterioles due to cilnidipine was markedly suppressed by the pretreatment with ω-conotoxin GVIA, a selective inhibitor of N-type calcium channels (*21*). Further, a renal micropuncture study in L-NAME-exacerbated SHR has shown that cilnidipine decreases glomerular capillary pressure, and afferent and efferent arteriolar resistance (*15*). These results indicate that cilnidipine dilates efferent arterioles by blocking N-type calcium channels of renal nerve endings, leading to reduced pressure load on the glomeruli.

The increase in serum Cr in the cilnidipine group appears to signify a functional decrease in intraglomerular pressure due to efferent arteriolar dilatation. On the other hand, amlodipine dilated mainly afferent arterioles, leading to glomerular hypertension and an increase in proteinuria. It has been reported that the pressure load on the renal glomeruli is profoundly involved in the progression from glomerular diseases to chronic renal failure. In the African American Study of Kidney Disease and Hypertension (AASK) trial, in which patients with hypertensive renal disease were enrolled, a significantly greater increase in proteinuria was observed in the amlodipine group than in the ACE inhibitor group, and the trial in the amlodipine group was discontinued (*2*). The current study, which included patients with chronic glomerulonephritis and diabetic nephropathy, showed a more than 50% increase in proteinuria in half of the patients who continued to receive amlodipine and, much like the AASK trial, suggested a risk of renal function deterioration due to amlodipine administration. However, because the duration of our study was only 12 months, we cannot conclude that the decrease in renal function in the cilnidipine group would be overcome by longer-term treatment. In the AASK trial (*2*), the treatment with amlodipine increased renal function during the initial 12 months. About 36 months were required until the renal function in the amlodipine group decreased to the level of that in the ramipril group.

In the current study, heart rate decreased by changing from other CCBs to cilnidipine, suggesting the ability of cilnidipine to suppress the reflex tachycardia due to other CCBs. This finding is in agreement with several previous studies (*22–25*) in which cilnidipine suppressed sympathetic nervous activity, especially under a stress-induced hyperactive condition.

An experiment in which N-type calcium channels were expressed in *Xenopus laevis* oocytes found that amlodipine also had N-type calcium channel inhibitory activity (*26*). However, the selectivity of cilnidipine for N-type calcium channels, shown as the ratio of IC_{50} of CCB for N-type and L-type channels, was about 50 times that of amlodipine (*27*). In humans, amlodipine-induced blood pressure reduction is known to increase skeletal muscle sympathetic-nerve activity (28). In addition, myocardial scintigraphy with ^{123}I-*m*-iodobenzylguanidine showed that cilnidipine suppressed cardiac sympathetic activity to a greater extent than amlodipine (*29*). We consider that the N-type calcium channel inhibitory activity of amlodipine is not as definite as that of cilnidipine.

In the current study, almost all patients were treated with a combination of CCB and RA inhibitors. The combined use of RA inhibitors and CCBs with excellent antihypertensive activity to achieve blood pressure control and organ protection is a useful regimen of antihypertensive drugs for patients with nephropathy (*30*, *31*). The combination of an ACE inhibitor and either a nondihydropyridine CCB (*30*) or amlodipine (*31*) reduced urinary protein excretion to a greater extent than the use of any of these drugs singly. In the former study (*30*), the decrease in proteinuria was explained by the reduction in the glomerular-size selectivity of proteinuria due to an ACE inhibitor and nondihydropyridine CCB. In the latter study (*31*), the greater reduction in albumin excretion was ascribed to the greater improvement in glomerular hypertension by the combination therapy. Since the mechanism by which cilnidipine dilates efferent arterioles is different from that of RA inhibitors, additive effects on efferent arteriolar dilatation and proteinuria can be expected by combination therapy with RA inhibitors. However, the effects on glomerular-size selectivity cannot be excluded in the current study.

The current study has several limitations. Despite the use of a randomized, prospective trial, the number of patients was small. Moreover, our study was not designed to assess the long-term effects of CCBs on deterioration of renal function. Further large-cohort and longer-term studies will be needed to demonstrate the reno-protective effects of cilnidipine.

In conclusion, the current study suggests that the effects of CCBs on proteinuria and renal function vary with the antagonist class. Cilnidipine and other CCBs may reduce proteinuria *via* their dilation of the efferent arterioles. Longer-term observation will be needed to clarify whether cilnidipine is superior to other CCBs in maintaining renal function.

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Relationship Between C-Reactive Protein and Progression of Early Carotid Atherosclerosis in Hypertensive Subjects

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Background and Purpose—Hypertensive outpatients were investigated for C-reactive protein (CRP) and carotid atherosclerosis because the influence of CRP on the progression of subclinical atherosclerosis in hypertensives remains unclear.

Methods—A total of 124 outpatients (aged 40 to 79 years) in treatment for hypertension were enrolled. They underwent repeated ultrasonographic evaluation of the carotid arteries for 35±12 months. Focal intima-media thickening of ≥1.1 mm was defined as plaque, and the plaque number, plaque score, and the sum of all plaque thickness were calculated.

Results—Multivariate linear regression analysis revealed that CRP, pulse pressure, and systolic blood pressure were related to the annual change of plaque number (β=0.34, 0.27, and 0.30; all $P<0.01$) and plaque score (β=0.38, 0.27, and 0.23; $P<0.001$, $P<0.01$, and $P<0.05$, respectively) independently of other risk factors. In 64 patients taking antihypertensive medications with a blood pressure of <140/90 mm Hg, CRP and the pulse pressure were related to the annual change of plaque number (r=0.40 and 0.26; $P<0.01$ and $P<0.05$, respectively) and plaque score (r=0.44 and 0.31; $P<0.001$ and $P<0.05$, respectively).

Conclusions—In hypertensive patients being managed by drug therapy or lifestyle modification, CRP is an equivalent or superior independent predictor of the progression of carotid atherosclerosis than the pulse pressure or systolic blood pressure. (***Stroke*. 2004;35:1625-1630.)**

Key Words: atherosclerosis ■ hypertension ■ carotid artery ■ inflammation ■ ultrasonography

Hypertension is 1 of the major traditional risk factors for atherosclerosis. The management of hypertension is very important, but its treatment and that of other traditional risk factors does not completely inhibit the development of atherosclerosis or prevent cardiovascular events.[1] Atherosclerosis is now considered to be partly attributable to an inflammatory response,[2] and there is evidence of a link between atherosclerosis[3,4] or cardiovascular disease (CVD)[5,6] and elevated serum levels of C-reactive protein (CRP). With regard to the contribution of CRP to the relationship between hypertension and CVD, a recent study showed that the risk of myocardial infarction was marginal in hypertensives without a simultaneous high CRP level.[7] Several other inflammatory serum proteins are reported to be associated with an increased risk of stroke among men with a high systolic blood pressure (SBP).[8] New guidelines suggest that patients who have an intermediate risk of CVD based on traditional risk factors may benefit from the measurement of high-sensitivity CRP (hs-CRP).[9] However, there have been no reports about the influence of CRP on the progression of subclinical atherosclerosis in patients with hypertension. It is well known that the severity of carotid atherosclerosis is closely related to the presence of CVD and the risk of CVD events. In the present study, we tested hs-CRP and office blood pressure as predictors of the progression of carotid atherosclerosis in hypertensive patients.

Materials and Methods

Patients

Between September 1996 and March 1998, we examined outpatients aged 40 to 79 years who were attending the Department of Internal Medicine and Therapeutics at Osaka University Hospital for carotid atherosclerosis because of the presence of risk factors for CVD. Each patient gave written informed consent to the collection of blood samples and follow-up for at least 2 years to evaluate the development of carotid atherosclerosis. Patients were excluded from the study if they had experienced a cardiovascular event during the previous year (n=2) or if they had advanced carotid atherosclerosis (n=25) or other diseases that could increase the hs-CRP level (18 had aortitis, 2 had collagen diseases, 2 had malignant tumors, and 1 had chronic bronchitis). During the follow-up period, 8 patients experienced a new cardiovascular event, 5 of whom did not undergo follow-up carotid ultrasonography. Another 5 patients developed malignant tumors, and 2 patients were lost to follow-up. A total of 12

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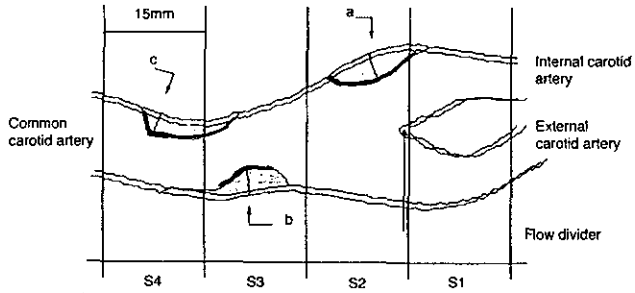

Figure 1. Diagram of carotid bifurcation and plaque score measurement obtained from B-mode ultrasonography. Plaque score was calculated by summing all plaque thicknesses in millimeters in each segment on both sides (a+b+c+contralateral plaques). Carotid artery was divided into 4 parts of 15 mm in length each from the flow divider (S1 to S4).

patients without follow-up carotid ultrasonography were deleted from the analysis. Ultimately, 179 patients were enrolled in the previous study, of whom 129 patients were hypertensives being treated with drug therapy or lifestyle modification. Information about antihypertensive therapy was missing for 5 patients, so this study presents data on the remaining 124 patients.

Risk Factors

Blood pressure was measured in the right arm with the patient in the seated position after a 5-minute rest, following recommendations of the American Heart Association.[10] The average of 2 consecutive blood pressure measurements was calculated. Hypertension was defined as an SBP of ≥140 mm Hg, a diastolic blood pressure (DBP) of ≥90 mm Hg, or current use of antihypertensive medications. The other traditional risk factors for CVD were classified as follows. Hypercholesterolemia was defined as a total cholesterol level of ≥220 mg/dL (5.69 mmol/L) or current cholesterol-lowering therapy. Diabetes mellitus was defined as a glycosylated hemoglobin A_{1c} concentration of >5.8% or current use of oral hypoglycemic agents. Body mass index was the weight in kilograms divided by the square of the height in meters. Patients were categorized as smokers if they were current smokers or had stopped smoking <1 month before entry into the study. Cigarette pack years were calculated for each patient as a measure of cumulative smoking exposure. Patients were categorized as having CVD if there was a history of cerebrovascular disease, ischemic heart disease, aortic aneurysm, or peripheral vascular disease.

Evaluation of Carotid Atherosclerosis

To evaluate the progression of carotid atherosclerosis, high-resolution B-mode ultrasonography using a 7.5-MHz duplex probe (EUB-525, Hitachi) was performed repeatedly over a period of ≥2 years. Baseline and follow-up ultrasound images were recorded on VHS videotape, and the changes of each plaque were evaluated in a blinded manner. The method was similar to that used by us in another prospective study.[3,11] On the basis of our previous findings, the upper limit of normal for the intima-media thickness (IMT) was set at 1.0 mm, and areas with an IMT of ≥1.1 mm were defined as atheromatous plaques. The plaque score was calculated by summing the thickness of all plaques measured in both carotid arteries (Figure 1),[12] and we used the number of plaques and the plaque score to estimate the severity of carotid atherosclerosis. The progression of atherosclerosis was estimated by inserting each parameter into the following formula: Δ value/year=(final value−baseline value)/years of follow-up. Advanced carotid atherosclerosis was defined as a plaque score of >10,[11] and such patients were not enrolled in this study.

Measurement of the Circulating hs-CRP Concentration

Blood samples were collected in tubes containing citric acid and stored at −80°C after centrifugation. The stored serum for each patient was thawed in April 1998 for hs-CRP measurement using an automatic immunonephelometer with a sensitivity of 0.02 mg/dL (Behring NA latex CRP; Behring Institute).

Statistical Analysis

Natural log transformation of the hs-CRP data achieved a normal distribution, so log-transformed hs-CRP values were used. All hs-CRP concentrations below the detection limit were assigned a log-transformed value of −4.605 (ie, an hs-CRP value of 0.01 mg/dL). The relationship between measured risk factors, including log-transformed CRP values, and the parameters of carotid atherosclerosis was evaluated by calculation of Pearson correlation coefficients. Spearman rank correlation coefficients were used for the skewed distribution of cigarette pack years. Student *t* test was used to evaluate the difference between the parameters in relation to the presence and absence of categorized traditional risk factors, including treatment with statins, aspirin, or angiotensin-converting enzyme (ACE) inhibitors. Multiple linear regression analyses were performed to assess the contribution of CRP to the prediction of annual changes of each parameter compared with the contribution of hypertension and other traditional risk factors. Two-way ANOVA with Newman–Keuls test was used to estimate between-group differences of parameters of carotid atherosclerosis in relation to hs-CRP and blood pressure. Probability values (2-tailed) of <0.05 were considered significant. For 2-way ANOVA test, Statistica for Windows R 5.5 (StatSoft) was used. The other statistical analyses were performed with SPSS for Windows version 9.0J.

Results

The baseline characteristics of the 124 subjects are summarized in Table 1. The follow-up period was 35±10 months. With regard to the relationships between hs-CRP and traditional risk factors, there was a significant association of the hs-CRP level with age (r=0.22; P<0.05), fasting blood glucose (r=0.19; P<0.05), and high-density lipoprotein cholesterol (r=−0.19; P<0.05). The relationship of CRP with cigarette pack years (r=0.17; P=0.059), pulse pressure (r=0.17; P=0.060), and SBP (r=0.15; P=0.086) was also positive but showed no statistical significance. There was no significant relationship between the hs-CRP level and the other traditional risk factors. Sex and the presence or absence of risk factors and treatment with ACE inhibitors, statins, or aspirin had no significant influence on the hs-CRP levels.

Among categorized risk factors, men had further progression than women (0.76±1.18 versus 0.43±1.00 in annual change of plaque score; P<0.05). The relationships between hs-CRP, pulse pressure, SBP, DBP, and the parameters of carotid atherosclerosis are shown in Table 2. Pulse pressure, SBP, and hs-CRP were correlated with the annual changes of plaque number and plaque score in simple regression analysis, and the correlations remained significant after adjusting for the effect of other traditional risk factors and for the baseline severity of carotid atherosclerosis. No other traditional risk factors (including DBP) were significantly correlated with the parameters of carotid atherosclerosis in simple regression analysis. When analysis was limited to the patients without hypercholesterolemia, diabetes mellitus, or current smoking, the results were similar to those in the total patient population, except that there was no significant association with SBP in the nonhypercholesterolemic or nondiabetic subgroups (Table 2). The progression of carotid atherosclerosis in relation to pulse pressure/SBP and hs-CRP is shown in Figures 2 and 3, respectively. Patients were divided into 2

TABLE 1. Baseline Characteristics of the Patients (n=124)

Age, y	62.7±8.7
Male	66 (53)
Antihypertensives medication	102 (82)
ACEI/CCB/β-blocker	33 (27)/74 (60)/37 (30)
α-blocker/diuretics	11 (9)/5 (4)
SBP/DBP, mm Hg	139±16/83±11
Pulse pressure, mm Hg	56±15
Hypercholesterolemia/statin medication	48 (39)/26 (21)
Total/HDL cholesterol, mg/dL (mmol/L)	205±31/58±15 (5.3±0.8/1.5±0.4)
Diabetes mellitus/oral hypoglycemic agents	21 (17)/4 (3)
Fasting blood glucose, mg/dL (mmol/L)	104±29 (5.8±1.6)
Hemoglobin A_{1c}, %	5.3±0.8
Body mass index, kg/m^2	23.7±2.8
Current smoker	14 (11)
Cigarette pack years	0 (0, 6.0) [10.0]
History of CVD	36 (29)
Antiplatelet medication/aspirin medication	25 (20)/7 (6)
CRP, mg/dL	0.07 (0.04, 0.15)
Plaque No.	1.0 (0, 3.0) [2.4]
Plaque score	2.4 (0, 4.5) [3.9]

The age, blood pressure, cholesterol, fasting blood glucose, hemoglobin A_{1c}, and body mass index are shown as mean±SD. Data on the blood pressure, cholesterol, fasting blood glucose, and hemoglobin A_{1c} are shown for all 124 patients. Cigarette pack years, CRP, plaque no., and plaque score are shown as the median and interquartile range. The mean values of cigarette pack years for past and current smokers and the mean plaque no. and plaque score for the patients with carotid atherosclerosis are shown in square brackets. Other values are the no. of patients, along with the proportion in parentheses.

ACEI indicates ACE inhibitor; CCB, calcium channel blocker.

TABLE 2. Association Between hs-CRP, Blood Pressure, and Parameters Associated With the Development of Carotid Atherosclerosis

		Simple Regression		Multivariate Regression* (Standardized)	
		r	*P*	β	*P*
In total patients (n=124)					
ΔPN/yr	hs-CRP	0.314	<0.001	0.343	0.001
	Pulse pressure	0.281	0.002	0.267	0.006
	SBP	0.290	0.001	0.299	0.001
	DBP	0.054	0.557	0.000	0.999
ΔPS/yr	hs-CRP	0.328	<0.001	0.376	<0.001
	Pulse pressure	0.287	0.001	0.268	0.005
	SBP	0.238	0.008	0.227	0.014
	DBP	−0.031	0.736	−0.104	0.299
ΔPS/yr per subgroup					
Patients without hypercholesterolemia (n=76)					
hs-CRP		0.343	0.002	0.452	0.001
Pulse pressure		0.274	0.017	0.282	0.034
SBP		0.210	0.068	0.148	0.235
Patients without diabetes mellitus (n=103)					
Hs-CRP		0.283	0.004	0.424	<0.001
Pulse pressure		0.256	0.009	0.326	0.004
SBP		0.180	0.070	0.185	0.080
Noncurrent smoker (n=110)					
Hs-CRP		0.258	0.006	0.310	0.005
Pulse pressure		0.316	0.001	0.331	0.002
SBP		0.268	0.005	0.391	0.002

ΔPN/yr indicates annual change of plaque number; ΔPS/yr, annual change of plaque score.

*Each parameter of blood pressure, together with hs-CRP and other traditional risk factors, was used as an independent variable in each multivariate regression model. The standardized β and *P* values of hs-CRP in Table 2 are adjusted for pulse pressure, age, sex, total cholesterol, hemoglobin A_{1c} cigarette pack years, body mass index, the severity of carotid atherosclerosis, and uses of ACE inhibitor, statin, and aspirin. When SBP or DBP was used instead of pulse pressure as a parameter of blood pressure, the standardized β and *P* values of hs-CRP were similar to those in Table 2. hs-CRP indicates high sensitivity C-reaction protein; ΔPS/y, annual change of plaque score.

groups at the median pulse pressure (53 mm Hg), an SBP of 140 mm Hg, and an hs-CRP value of 0.12 mg/dL. We reported previously that annual rate of increase in carotid atherosclerosis was accelerated in patients with an hs-CRP value of ≥0.12 mg/dL.[3] Patients with higher hs-CRP levels had greater progression of atherosclerosis than those with lower hs-CRP levels in both the lower and higher pulse pressure groups and even in patients with an SBP of <140 mm Hg on antihypertensive therapy. When analysis was limited to the 64 patients with blood pressure of <140/90 mm Hg on antihypertensive therapy, the relationship between hs-CRP and carotid atherosclerosis was stronger than that for pulse pressure. There were no significant relationships between the other traditional risk factors (including SBP and DBP) and the annual changes of plaque number or plaque score, except for body mass index (Table 3).

Discussion

This is the first study to demonstrate that evaluation of CRP could be equal or superior for predicting the development of carotid atherosclerosis to measurement of the pulse pressure or SBP in hypertensives and that its predictive value is independent of blood pressure. With respect to the association between blood pressure and carotid atherosclerosis, to the best of our knowledge, there have been few longitudinal studies focused on the middle-aged and elderly population.[13,14] These studies have emphasized an elevated pulse pressure and SBP as risk factors for atherosclerosis. Similar to the results of such studies, our findings suggested that pulse pressure and SBP are related to the progression of carotid atherosclerosis. It is thought that an elevated pulse pressure causes greater stretching of the arteries, which induces fatigue and fracture of the elastic elements and thus is likely to hasten the development of intimal damage that leads to atherosclerosis.[15] The Framingham study demonstrated a link between cardiovascular mortality and pulse

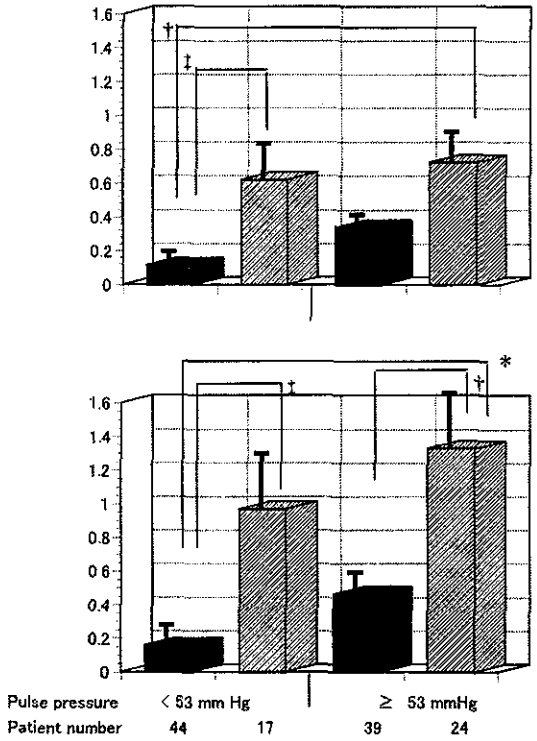

Figure 2. The annual changes of plaque number (top) and plaque score (bottom) in relation to pulse pressure and hs-CRP. ▨hs-CRP ≥0.12 mg/dL. ■hs-CRP< 0.12 mg/dL. Bars represent mean values and lines represent the SEM. *P<0.001; †P<0.01; ‡P<0.05.

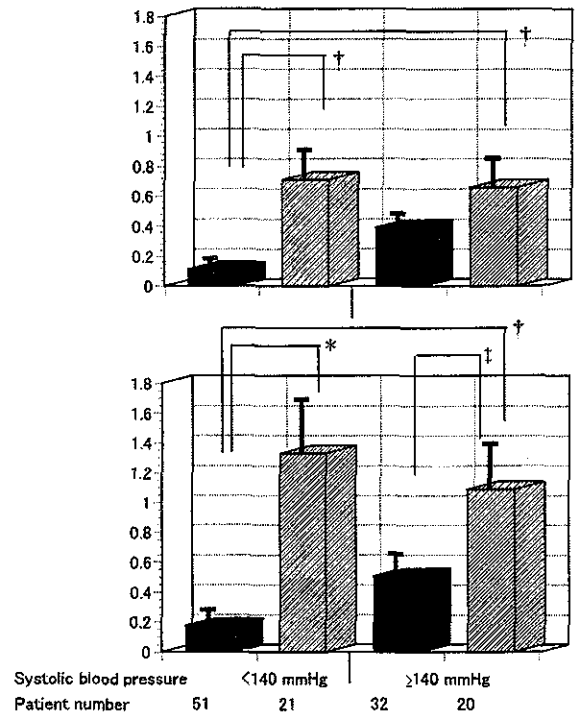

Figure 3. The annual changes of plaque number (top) and plaque score (bottom) in relation to SBP and hs-CRP. ▨hs-CRP ≥0.12 mg/dL. ■hs-CRP< 0.12 mg/dL. Bars represent mean values and lines represent the SEM. *P<0.001; †P<0.01; ‡P<0.05.

pressure by longitudinal follow-up of persons >50 years old.[16] Another large-scale study revealed similar results in male subjects aged 40 to 69 years,[17] whereas the age of the present study population was similar. We found that there was no significant relationship between the other traditional risk factors (including DBP) and the progression of carotid atherosclerosis. The lack of an association with these risk factors in the present study can be partly explained by the influence of drug therapy and lifestyle modification or the low statistical power of our analysis. The age of the present study population may also help to explain the lack of an association between DBP and carotid atherosclerosis.

Multivariate analysis revealed that CRP was one of the independent predictors of the progression of carotid atherosclerosis. Subset analysis excluding each traditional risk factor showed a similar result. One possible reason that a high CRP level is associated with carotid atherosclerosis indepen-

TABLE 3. Association Between hs-CRP Concentration, Blood Pressure, and Parameters Associated With the Development of Carotid Atherosclerosis in 64 Hypertensive Patients With Blood Pressure of <140/90 mm Hg on Antihypertensive Therapy

	Simple Regression			
	ΔPN/yr		ΔPS/yr	
	r	*P*	*r*	*P*
hs-CRP	0.404 (0.23, 0.91)	0.002	0.436 (0.48, 1.80)	<0.001
Pulse pressure	0.264 (0.015, −0.34)	0.044	0.310 (0.05, −1.8)	0.016
SBP	0.225	0.086	0.237	0.069
DBP	−0.007	0.958	−0.040	0.761
Age	−0.198	0.134	−0.183	0.162
Total cholesterol	0.078	0.558	0.011	0.931
Hemoglobin A_{1c}	−0.021	0.882	−0.016	0.907
Cigarette pack years	0.004	−0.977	0.012	0.930
Body mass index	0.334 (0.048, −0.73)	0.010	0.272 (0.12, −2.36)	0.035

ΔPN/yr indicates annual change of plaque number; ΔPS/yr, annual change of plaque score. The values in parentheses show the regression coefficient and intercept.

dently of blood pressure and other traditional risk factors may be the tight linkage of CRP with atherosclerotic processes. For example, CRP may contribute to monocyte recruitment in atherogenesis[18] and to induction of tissue factor release by monocytes, which is potentiated by interferon-γ and lipopolysaccharide.[19] CRP has a direct influence on atherosclerotic vessels by activation of the complement system, thereby promoting inflammation and thrombosis.[20] A recent clinical study showed that CRP was significantly correlated with the calculated 10-year Framingham coronary heart disease risk (FCHDR) but was weakly correlated with most individual components of the FCHDR score.[21] This suggested that CRP may capture different components than the traditional components of coronary risk reflected in the FCHDR score. Thus, monitoring of the blood pressure is important but not enough to predict the development of atherosclerosis in hypertensives. The average of 2 consecutive office blood pressure measurements at 1 time point was representative of the blood pressure value in the present study. A recent study suggested that circadian SBP variability is the best independent predictor of the development of carotid atherosclerosis,[13] whereas a cross-sectional study revealed that target organ damage caused by hypertension is more closely related to the home blood pressure than the office blood pressure.[22] The serum level of CRP may partly reflect the circadian blood pressure pattern or home blood pressure, or may be an indicator of a step in the process of atherosclerosis itself,[9] making it equal or superior to office blood pressure measurement for the prediction of atherosclerosis.

Chronic inflammation may induce endothelial dysfunction, which is followed by further elevation of blood pressure (pulse pressure and SBP)[23] and the onset of cardiovascular disease.[24] Several studies have shown that CRP is an independent risk factor for hypertension,[25,26] so CRP, inflammation, and hypertension appear to be linked in the process of atherosclerosis. A recent study suggested that inflammation is important for accelerated progression of atherosclerosis, particularly in hypertensives.[8] Although the relationship of CRP with pulse pressure and SBP was positive in the present study, it did not reach statistical significance. This lack of a significant association might be attributable to the low statistical power of our analysis or use of antihypertensive medication by the subjects,[27] or it may indicate that the actual association is weak.[21]

It could be argued that our results were influenced by a selection bias of the patient population because most of them were on antihypertensive therapy and some had other traditional risk factors. However, the relationship of pulse pressure, SBP, and CRP with carotid atherosclerosis remained significant after adjusting for antihypertensive therapy and other traditional risk factors, and stratified analysis showed similar results. Recent guidelines have proposed that the entire adult population should not be screened for CRP measurement for purposes of cardiovascular risk assessment but that the measurement may be useful in selected patients, such as those estimated to have a moderate risk on the basis of the 10-year FCHDR.[9] The risk management in the present study population was similar to the FCHDR concept of moderate risk, and we demonstrated that CRP was equal or superior to the office blood pressure for predicting the progression of carotid atherosclerosis, with these parameters being independent of each other. In conclusion, measurement of CRP may be valuable for predicting the progression of carotid atherosclerosis in selected hypertensive patients who are already being treated by drug therapy or lifestyle modification.

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Original Article

Relationship between the Awareness of Salt Restriction and the Actual Salt Intake in Hypertensive Patients

Yuko OHTA, Takuya TSUCHIHASHI, Michio UENO, Tomoko KAJIOKA, Uran ONAKA, Mitsuhiro TOMINAGA, and Kimika ETO

A 24-h home urine collection was conducted to estimate accurate salt intake in hypertensive outpatients. Using 24-h urinary creatinine excretion as a criterion for success, urine samples were obtained from 534 hypertensive patients. The urinary salt excretion of hypertensive outpatients ranged widely from 1.5 to 23.4 g/day (mean value 9.7±3.9 g/day). Urinary salt excretion was higher in males than in females (10.6±4.0 *vs.* 9.2±3.7 g/day, $p<0.01$). Based on the questionnaires, the patients were divided into salt-conscious patients, or those who were careful to reduce their daily salt intake, and non-salt-conscious patients. It was found that urinary salt excretion was lower in the salt-conscious group than in the non-salt-conscious group (9.4±3.8 *vs.* 10.6±4.0 g/day, $p<0.01$), but that urinary salt excretion adjusted for body weight was not significantly different between the two groups (0.16±0.06 *vs.* 0.17±0.07 g/kg/day). Our results suggest that there was no obvious reduction in the actual salt intake in salt-conscious patients, suggesting the importance of monitoring salt intake by 24-h home urine collection and informing patients of their actual salt intake as a means of encouraging the achievement of salt restriction. (*Hypertens Res* 2004; 27: 243–246)

***Key Words*: salt restriction, 24-h home urine collection, urinary salt excretion, hypertension, salt intake**

Introduction

Extensive epidemiological literature has already documented the correlation between salt intake and blood pressure (BP) or the prevalence of hypertension (*1*, *2*). Salt restriction is now also widely promoted as an effective non-pharmacological approach to managing mild hypertension, as well as an important adjunct to pharmacological treatment in moderate and severe hypertension (*3*–*7*). The seventh report of the Joint National Committee (JNC 7) recommends sodium reduction to a level of no more than 100 mmol/day in hypertensive patients (*8*). Thus, it is recommended that physicians advise patients to reduce their salt intake, but the efficacy of this advice is questionable if patients' actual salt intake is not monitored. The aim of this study was to investigate urinary salt excretion and the relationship between the awareness of salt restriction and the actual salt intake in hypertensive outpatients.

Methods

We undertook 24-h home urine collection at first visit in 652 outpatients between January, 1998 and December, 1999. Twenty four-hour urine samples were collected using a partition cup (proportional sampling method (*9*)), which collects a 1/50 portion of the 24-h urine. If the 24-h creatinine excretion was within ±30% of the estimated values, the urine collection was considered successful. If the urine collection was judged to be unsuccessful, the patients were asked to try again. Patients who failed to complete the 24-h urine collection, in spite of possible repeated collection, were excluded from further analysis. BP was measured with a sphygmomanometer by the doctors while the patients were seated. Hypertension was considered to be present in patients with systolic blood pressure (SBP)≥140 mmHg and/or diastolic

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Table 1. Characteristics in Male and Female Patients

	All	Males	Females
Number of patients	534	211	323
Age (years)	58.3±11.6	58.0±12.9	58.5±10.6
BW (kg)	61.3±11.2	68.1±11.1**	56.9±8.9
BMI (kg/m^2)	24.3±3.5	24.6±3.3	24.1±3.6
SBP (mmHg)	144.0±12.5	144.3±13.0	143.9±12.2
DBP (mmHg)	87.4±7.7	87.9±7.8	87.0±7.7
Serum creatinine (mg/dl)	0.9±0.7	1.1±0.9**	0.7±0.4
Urinary salt excretion (g/day)	9.7±3.9	10.6±4.0**	9.2±3.7
Urinary salt excretion adjusted for BW (g/kg/day)	0.16±0.06	0.16±0.06	0.16±0.07
Antihypertensive drug (%)	49.6	52.1	48.0
Family history of hypertension (%)	47.6	51.7	44.9
Diabetes mellitus (%)	12.2	13.3	11.5

Values are means±SD. ** $p<0.01$ *vs.* females. BW, body weight; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

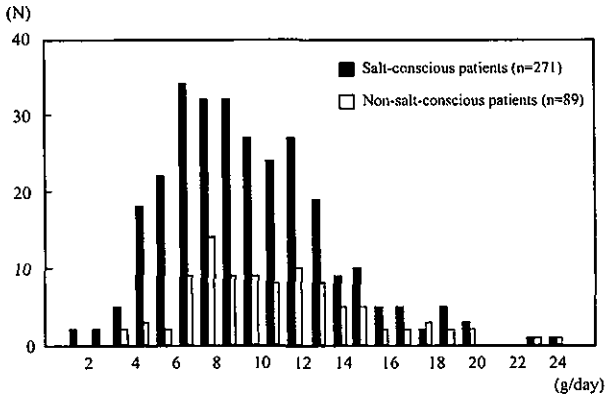

Fig. 1. *The distribution of 24-h urinary salt excretion in salt-conscious and non-salt-conscious patients.*

blood pressure (DBP)≥90 mmHg, or those patients on antihypertensive medication. The patients were asked, by questionnaire, about aspects of their lifestyle, such as habitual alcohol intake, smoking, and exercise, and were also asked whether they were conscious of salt, calorie and fat restrictions. The protocol was explained in detail, and informed consent was obtained from each patient.

Statistical Analysis

Values are presented as the means±SD. The differences in the variables were compared by one-way ANOVA. A χ^2 test was also utilized when appropriate. P values less than 0.05 were considered statistically significant.

Results

Among the 652 patients enrolled in this study, 534 patients successfully collected 24-h urine samples.

Characteristics in male and female patients are shown in Table 1. The patients had a mean age of 58.3±11.6 (26–90) years, and a mean BP of 144.0±12.5/87.4±7.7 mmHg. There were no differences in age, body mass index (BMI), BP, or prevalence of patients receiving antihypertensive drugs between males and females. Body weight and urinary salt excretion were significantly higher in males than in females. However, urinary salt excretion adjusted for body weight was similar between the two groups.

The questionnaire on the awareness of salt restriction was obtained from 360 patients. As shown in Fig. 1, the values of the 24-h urinary salt excretion were distributed widely, ranging from 1.5 to 23.4 g/day. Comparisons of the characteristics between the patients who were careful to reduce their daily salt intake (salt-conscious group, $n=271$) and the non-salt-conscious group ($n=89$) are presented in Table 2. There were no differences in BMI and frequency of family history of hypertension between the two groups. The salt-conscious group was older than the non-salt-conscious group, and there was a higher prevalence of females. This group also showed a lower BP and a higher prevalence of being on antihypertensive medication. Urinary salt excretion was significantly lower in the salt-conscious group than in the non-salt-conscious group (9.4±3.8 *vs.* 10.6±4.0 g/day, $p<0.01$), but urinary salt excretion adjusted for body weight was not significantly different between the groups.

Table 2. Characteristics in the Salt-Conscious and Non-Salt-Conscious Groups

	Salt-conscious group	Non-salt-conscious group
Number of patients	271	89
Men (%)	36.9††	55.0
Age (years)	59.7±11.3*	54.6±11.9
BW (kg)	60.5±11.6	63.8±12.2
BMI (kg/m^2)	24.2±3.6	24.5±3.7
SBP (mmHg)	141.0±10.4**	144.6±11.9
DBP (mmHg)	85.5±6.9**	87.9±7.1
Serum creatinine (mg/dl)	0.9±0.7	0.9±0.9
Urinary salt excretion (g/day)	9.4±3.8**	10.6±4.0
Urinary salt excretion adjusted for BW (g/kg/day)	0.16±0.06	0.17±0.07
Antihypertensive drug (%)	77.9**	60.7
Family history of hypertension (%)	73.1	62.9
Diabetes mellitus (%)	11.1	13.5

Values are means±SD. * $p<0.05$, ** $p<0.01$ *vs.* non-salt-conscious by ANOVA, †† $p<0.01$ *vs.* non-salt-conscious by χ^2 test. BW, body weight; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Discussion

The present study demonstrated that in hypertensive outpatients, there was no relationship between the awareness of salt restriction and the actual salt intake evaluated by 24-h urinary collection, which has been widely used to estimate dietary salt intake in epidemiological studies (*10–13*).

In the present study, urinary salt excretion was higher in males than in females, which may be attributable to the greater energy intake in males than females (*14*). In fact, males showed a higher body weight, and when urinary salt excretion was adjusted for body weight, urinary salt excretion was comparable between males and females.

It seems reasonable that BP and urinary salt excretion were significantly lower in the salt-conscious group than in the non-salt-conscious group. The characteristics of the two groups differ in sex and age. Thus, we may speculate that elderly and female individuals could be more aware than others of the importance of lifestyle modifications, such as salt restriction. However, no significant difference was found in urinary salt excretion adjusted for body weight between the salt-conscious and non-salt-conscious groups. This observation indicates that awareness of the necessity of salt restriction may not lead to an actual reduction of salt intake. Salt intake by the Japanese population has traditionally been high, although it has been decreasing in recent years. The National Nutrition Survey in Japan showed that the salt intake was 11.5 g in 2001 (*15*). The difficulty in achieving long-term dietary salt restriction might be attributable to the difficulty in changing the dietary habits of the Japanese. It has also been pointed out that although there has been an increase in variety in the Japanese diet, there is now a greater reliance on dining out, and the consumption of fast foods is increasing (*12*, *16*). These trends in the dietary habits of Japanese may also make it difficult to reduce salt intake.

With regard to seasonal variation, urinary salt excretion tended to decrease in summer (*17*). In the present study, 24-h urine collection was performed throughout the year in both groups. Thus, it seems unlikely that the seasonal variation of urinary salt excretion influenced the principal results of this study.

Doctors advise all hypertensive patients to reduce their salt intake, but it is important to evaluate whether patients follow this advice. Some methods have been proposed to improve compliance with dietary salt restriction. One study indicated that group management, in which feedback is provided to patients on their urinary salt excretion, was more effective in decreasing dietary salt intake than advice given without this support, or through an intensive educational effort by doctors and clinics (*18*). Another study showed that self-monitoring of urinary salt excretion at home, using chloride titrator strips, could, in conjunction with dietary counseling, facilitate compliance with a reduced salt intake (*19*). However, another report indicated that short counseling sessions with advice on salt restriction were not successful in producing dietary changes (*5*). Taken together, these results suggest that repeated monitoring of urinary salt excretion, along with providing feedback to patients, is the most important and practical way to achieve the reduction of salt intake in individual hypertensives.

In conclusion, there was no obvious reduction in actual salt intake in salt-conscious patients in the present study, suggesting the importance of monitoring salt intake and informing patients of their actual salt intake as a means of encouraging the achievement of salt restriction.

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