occurrence of ADRs.

Characteristics of subjects analyzed: The baseline characteristics of the 314 subjects are summarized in Table I. A total of 155 (49.4%) were male and 156 (49.7%) were elderly (≥ 65 years). The majority (265; 84.4%) were treated for primary prevention including 3 (1.0%) in category I (low risk), 111 (35.4%) in category II (middle risk), and 151 (48.1%) in category III (high risk), while only 49 (15.6%) were treated for secondary prevention, based on the JASGL2007. In addition, 205 (65.3%) patients had hypertension and 138 (44.0%) patients had diabetes mellitus (including impaired glucose tolerance). At 12 months, the mean (SD) daily dose was 7.7 (2.8) mg for rosuvastatin and 14.5 (5.0) mg for pravastatin.

Changes in lipid parameters and carotid mean-IMT: The changes between the baseline and 12-month data for key parameters, including lipids, HbA1c, and carotid mean-IMT are summarized in Table II. The lipid parameters showed decreases in LDL-C, TG, LDL-C/HDL-C ratio, and non-HDL-C, and an increase in HDL-C. The carotid mean-IMT showed a marginal increase in the actual measurement (+0.020 mm).

Correlation analyses for mean-IMT: The results of simple correlation analyses between mean-IMT change at 12 months and each explanatory variable are presented in Table III. No explanatory variable indicated significant correlation to mean-IMT change at baseline. At the 12-month measurement point, mean-IMT change was correlated with LDL-C ($R = 0.187$; $P = 0.0016$), LDL-C/HDL-C ratio ($R = 0.152$; $P = 0.0105$), and non-HDL-C ($R = 0.132$; $P = 0.0259$). In addition, for the percent changes after 12 months of treatment, mean-IMT change

Table I. Baseline Characteristics of the Subjects in the Subanalysis

	Overall $n = 314$
Sex, Male (%)	155 (49.4)
Age (years: Mean ± SD)	63.6 ± 9.0
Elderly, ≥ 65 years (%)	156 (49.7)
Blood pressure (Mean ± SD)	
SBP (mmHg) (*n*)	131.7 ± 17.5 (314)
DBP (mmHg) (*n*)	75.8 ± 12.4 (314)
JASGL2007 category (%)	
Primary prevention	265 (84.4)
Category I	3 (1.0)
Category II	111 (35.4)
Category III	151 (48.1)
Secondary prevention	49 (15.6)
CHD risk factors (%)	
Family history of premature CHD	55 (17.5)
Smoking	61 (19.4)
Medical history (%)	
Hypertension	205 (65.3)
Diabetes mellitus	138 (44.0)
Low HDL-C	26 (8.3)
Cerebral infarction	16 (5.1)
Cerebral hemorrhage	0 (0)
Arteriosclerosis obliterans	6 (1.9)
Coronary disease	49 (15.6)
Mean daily dose of statins at 12 months (mg)	
Rosuvastatin (Mean ± SD: *n*)	7.7 ± 2.8 (159)
Pravastatin (Mean ± SD: *n*)	14.5 ± 5.0 (155)
Concomitant drug (%)	
Antihypertensive drug	175 (55.7)
Antidiabetic drug	76 (24.2)

Baseline characteristics of the 314 subjects are summarized. The subjects had enrolled in the preceding JART Study and had an IMT ≥ 1.1 mm measured by carotid artery ultrasound and statin treatment for ≥ 1 year. The subjects were eligible for evaluation of the relationship between LDL-C and carotid mean-IMT change. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; JAS, Japan Atherosclerosis Society; GL, guideline; CHD, coronary heart disease; and HDL, high-density lipoprotein.

Table II. Baseline and 12-Month Data for the Key Parameters

	Baseline		12-month	
LDL-C (mg/dL)* (*n*)	164.4 ± 30.0	(309)	100.7 ± 28.8	(289)
HDL-C (mg/dL) (*n*)	54.5 ± 12.7	(311)	58.1 ± 14.4	(291)
TG (mg/dL) (*n*)	142.9 ± 75.5	(311)	125.0 ± 63.5	(291)
LDL-C/HDL-C ratio	3.2 ± 1.0	(309)	1.8 ± 0.7	(289)
Non HDL-C (mg/dL) (*n*)	192.4 ± 32.1	(311)	125.4 ± 31.9	(291)
HbA1c [NGSP] (%) (*n*)	6.25 ± 0.84	(302)	6.30 ± 0.84	(286)
Carotid mean-IMT (mm) (*n*)	0.893 ± 0.209	(310)	0.913 ± 0.188	(292)

Comparisons between the baseline and 12-month data for key parameters including lipids, HbA1c, and carotid mean-IMT are summarized. The lipid parameters and carotid mean-IMT change show significant changes, except for HbA1c and carotid mean-IMT. The statistical comparisons were performed using a non-paired *t*-test, except for the carotid mean-IMT change, which was analyzed by a test of population mean (= 0). The significance level of the statistical tests was $\alpha = 0.05$. The adjustment of multiplicity was not applied. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; HbA1c, hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program; and IMT, intima-media thickness. * LDL-C level was calculated using Friedewald's formula as follows: LDL-C = total cholesterol (TC) – HDL-C – TG/5.

Table III. Simple Correlations Between Mean-IMT Change and Key Variables at 12 Months

Explanatory variable	*R*	Standardized *R*	*P*
At 12 months			
TC	0.04086	0.113	0.0566
LDL-C	0.07546	0.187	0.0016*
HDL-C	–0.03210	–0.040	0.5043
TG	–0.00788	–0.043	0.4676
LDL-C/HDL-C ratio	2.47086	0.152	0.0105*
Non HDL-C	0.04812	0.132	0.0259*
HbA1c	–0.33012	–0.024	0.6902
SBP	0.05125	0.058	0.3249
DBP	0.01182	0.010	0.8692
Percent changes after 12 months			
TC	0.04771	0.056	0.3471
LDL-C	0.08303	0.130	0.0294*
HDL-C	–0.04507	–0.070	0.2436
TG	–0.02143	–0.077	0.1944
LDL-C/HDL-C ratio	0.08208	0.138	0.0208*
Non HDL-C	0.06000	0.087	0.1431
HbA1c	–0.01338	–0.006	0.9228
SBP	0.00751	0.009	0.8760
DBP	–0.00131	–0.002	0.9754

The results of simple correlation analyses between mean-IMT change at 12 months and each explanatory variable are presented. At the 12-month measurement point, mean-IMT change is correlated with LDL-C, LDL-C/HDL-C ratio, and non-HDL-C. For the percent changes after 12 months of treatment, mean-IMT change is correlated with LDL-C and LDL-C/HDL-C ratio. The correlation coefficients were tested by a test of the null correlation ($R = 0$) with a significance level of $\alpha = 0.05$. * Significant difference in a test of the null correlation ($R = 0$) ($\alpha = 0.05$). IMT indicates intima-media thickness; *R*, correlation coefficient; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

was correlated with LDL-C ($R = 0.130$; $P = 0.0294$) and LDL-C/HDL-C ratio ($R = 0.138$; $P = 0.0208$).

The data for carotid mean-IMT at 12 months were divided into 4 subgroups based on the corresponding LDL-C at 12 months, as < 80, ≥ 80 to < 100, ≥ 100 to < 120, and ≥ 120 mg/dL, in consideration of the JASGL2007 and NCEP ATP III categories. The results are summarized in the Figure. In subgroup 1 (LDL-C of < 80 mg/dL), the median mean-IMT change was –1.35% and –0.010 mm. In subgroup 2 (LDL-C of ≥ 80 to < 100 mg/dL), the median mean-IMT change was 0.46% and 0.005 mm. In subgroup 3 (LDL-C of ≥ 100 to < 120 mg/dL), the median mean-IMT change was 4.29% and 0.040 mm. Finally, in subgroup 4 (LDL-C of ≥ 120 mg/dL), the median mean-IMT change was 3.42% and 0.035 mm. A trend analysis using the Jonckheere–Terpstra test showed statistical significance ($P = 0.0002$). Subgroup 1 showed the lowest mean-IMT change in the median and the values (–1.35%, –0.010 mm) shifted to "Minus". Although subgroup 3 showed the highest mean-IMT change in the median (4.29%) which was higher than that of subgroup 4 (3.42%), the trend of medians indicated subgroup 1 < 2 < 3. As a reference, mean-IMT for subjects whose LDL-C reached < 70 mg/dL ($n = 37$) was –3.75% (–0.030 mm) of median with –16.67% of 10 percentile, 9.59% of 90 percentile, –6.45% of first quarter and 4.00% of third quarter.

Similarly, the data for the carotid mean-IMT after 12 months were divided into 4 subgroups (quartiles) by the corresponding LDL-C absolute change from baseline, as < –85, ≥ –85 to < –60, ≥ –60 to < –45, and ≥ –45 mg/dL. The lowest was subgroup 1 (1 Q: LDL-C change of < –85 mg/dL) with a median mean-IMT change of –1.72%. A trend analysis using the Jonckheere–Terpstra test showed statistical significance ($P = 0.0014$).

Safety: The frequencies of ADRs in each subgroup are summarized in Table IV. The total numbers of subjects with any ADR were similar in subgroup 1 (6; 7.69%), subgroup 2 (6; 9.09%), and subgroup 4 (6; 8.00%), but lower in subgroup 3 (1; 1.43%). No clinically significant deviation was observed. In addition, the safety profile of the LDL-C < 70 mg/dL subgroup ($n = 39$), which is recommended in the NCEP ATP III categories, showed no clinically significant ADRs (data not shown). One patient in subgroup 4 who received pravastatin experienced rhabdomyolysis as a serious ADR.

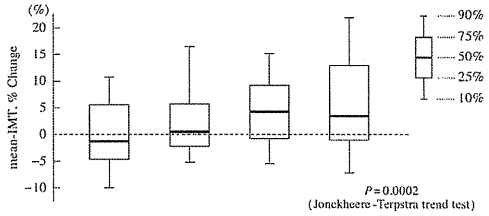
Discussion

In the preceding JART Study, intensive lipid-lowering therapy with rosuvastatin slowed the mean-IMT progression more effectively than conventional therapy with pravastatin in Japanese patients within a relatively short treatment period. In this subanalysis, based on the results of the JART Study, we evaluated the extent to which intensive lipid-lowering therapy slowed the mean-IMT progression using a correlation analysis between LDL-C and mean-IMT change after 12 months of statin treatment.

The comparisons between the baseline and 12-month data for key parameters, including lipids, HbA1c, and carotid mean-IMT, are summarized in Table II. Simple correlation analyses were conducted to evaluate which parameter was mainly correlated to the change of mean-IMT, prior to correlation analysis between changes of mean-IMT and LDL-C level. Because no parameter exhibited a correlation at baseline, the change of mean-IMT did not depend on the subjects' background. However, LDL-C, LDL-C/HDL-C ratio, and non HDL-C showed significant correlations at 12-months. Therefore, we focused on LDL-C in this subanalysis because the other two parameters were both strongly related to LDL-C.

Our subanalysis successfully revealed the relationship between the therapeutic target for LDL-C and the mean-IMT change (Figure). Even for prevention in Japanese patients who have lower risk than Western patients, lowering the LDL-C level to below the therapeutic target prevented the mean-IMT progression more strongly. To be more precise, a lower achieved LDL-C level was associated with a smaller change of mean-IMT, and in particular, an LDL-C level lower than 80 mg/dL or 70 mg/dL induced a slowing of the progression of atherosclerosis as well as induction of regression of atherosclerosis. Actually, in subgroup 1 (LDL-C of < 80 mg/dL), the median mean-IMT change was negative (–1.35%), suggesting that the therapeutic target for LDL-C of < 80 mg/dL had a reduction effect on atherosclerosis. Another subgroup (LDL-C of < 70 mg/dL) showed a much lower mean-IMT change in the median (–3.75%, –0.030 mm), and these results support the NCEP ATP III criteria. A similar relationship between the absolute change of LDL-C from baseline and the mean-IMT change can be observed.

Atherosclerosis is deeply involved in the development of stroke[2] and CAD,[3,4] while the progression of atherosclerosis is deeply involved in dyslipidemia, especially the LDL-C level. The JASGL2007 criteria are typically used as the target levels for LDL-C control in primary and secondary prevention in Japan. Based on this guideline, the target level for LDL-C control in primary prevention for high-risk patients is < 120 mg/dL. The NCEP ATP III in the United States suggests a similar therapeutic target for LDL-C of < 100 mg/dL for high-risk patients. In the METEOR trial[16] and COSMOS study,[9] the serum LDL-C levels were lowered to approximately 80 mg/dL,



	LDL-C classification			
	< 80 n=75	80 ≤ < 100 n=66	100 ≤ < 120 n=67	≤ 120 n=74
mean-IMT, % Change (%)				
90 percentile	10.71	16.47	15.15	21.88
Q3	5.56	5.71	9.18	12.90
median (Q2)	−1.35	0.46	4.29	3.42
Q1	−4.65	−2.24	−0.79	−1.08
10 percentile	−10.00	−5.22	−5.43	−7.20
mean-IMT, Change (mm)				
median	−0.010	0.005	0.040	0.035

Figure. Trend analysis for mean-IMT change and LDL-C (% change) at 12 months. The data for the carotid mean-IMT after 12 months were divided into 4 subgroups based on the corresponding LDL-C level at 12 months, < 80, ≥ 80 to < 100, ≥ 100 to < 120, and ≥ 120 mg/dL. The distribution of the carotid mean-IMT in each subgroup is summarized as a box-and-whisker plot. A trend analysis using the Jonckheere–Terpstra trend test shows statistical significance ($P = 0.0002$). IMT indicates intima-media thickness; LDL, low-density lipoprotein; and Q, quarter.

Table IV. Comparison of Adverse Drug Reactions Among Subgroups Divided by LDL-C at 12 Months

	LDL-C at 12 months							
	< 80 $n = 78$		80 ≤ < 100 $n = 66$		100 ≤ < 120 $n = 70$		120 ≤ $n = 75$	
	n	%	*n*	%	*n*	%	*n*	%
Number of subjects with ADR	6	7.69	6	9.09	1	1.43	6	8.00
SOC PT								
Gastrointestinal disorders	1	1.28	2	3.03	0	0	0	0
abdominal discomfort	0	0	2	3.03	0	0	0	0
nausea	1	1.28	0	0	0	0	0	0
General disorders and administration site conditions	4	5.13	0	0	0	0	3	4.00
adynamia	2	2.56	0	0	0	0	0	0
discomfort	1	1.28	0	0	0	0	0	0
fatigue	1	1.28	0	0	0	0	2	2.67
peripheral edema	0	0	0	0	0	0	1	1.33
Hepatobiliary disorders	1	1.28	0	0	0	0	0	0
abnormal hepatic function	1	1.28	0	0	0	0	0	0
Infections and infestations	0	0	0	0	0	0	1	1.33
cystitis	0	0	0	0	0	0	1	1.33
Investigations	4	5.13	2	3.03	0	0	3	4.00
ALT increased	1	1.28	1	1.52	0	0	1	1.33
AST increased	0	0	1	1.52	0	0	0	0
CPK increased	1	1.28	0	0	0	0	1	1.33
γ-GT increased	2	2.56	0	0	0	0	0	0
positive RBC in urine	0	0	0	0	0	0	1	1.33
Metabolism and nutrition disorders	1	1.28	0	0	0	0	0	0
impaired glucose tolerance	1	1.28	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	2	2.56	4	6.06	1	1.43	4	5.33
arthralgia	1	1.28	1	1.52	0	0	1	1.33
back pain	0	0	1	1.52	0	0	0	0
myalgia	1	1.28	1	1.52	0	0	0	0
rhabdomyolysis	0	0	0	0	0	0	1	1.33
heaviness	0	0	1	1.52	0	0	1	1.33
myotony	0	0	0	0	1	1.43	0	0
musculoskeletal stiffness	0	0	0	0	0	0	1	1.33
Nervous system disorders	0	0	1	1.52	0	0	2	2.67
encephalalgia	0	0	1	1.52	0	0	0	0
hemiparesis	0	0	0	0	0	0	1	1.33
somnolent	0	0	0	0	0	0	1	1.33
Renal and urinary disorders	1	1.28	0	0	0	0	0	0
hematuria	1	1.28	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	1	1.28	2	3.03	0	0	2	2.67
eczema	1	1.28	0	0	0	0	0	0
pruritus	0	0	1	1.52	0	0	1	1.33
generalized rash	0	0	0	0	0	0	1	1.33
pruritic rash	0	0	1	1.52	0	0	0	0
Number of subjects with serious ADR	0	0	0	0	0	0	1	1.33
SOC PT								
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	1	1.33
rhabdomyolysis	0	0	0	0	0	0	1	1.33

The frequencies of ADRs are summarized by subgroups divided by LDL-C at 12 months. ADRs were classified by the PT and SOC of MedDRA. The definition of an ADR is any adverse event in which causality with the medication cannot be ruled out. LDL indicates low-density lipoprotein; ADR, adverse drug reaction; SOC, system organ class; and PT, preferred term; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GT, glutamyl transpeptidase; and RBC, red blood cells.

and this lipid-lowering effect led to the slowing of progression or induction of regression of atherosclerosis. Although the current JAS guideline recommends lowering the LDL-C level to 100 – 160 mg/dL according to the risk category of the patient,[10] levels of 80, 100, and 120 mg/dL are considered to be potential thresholds for the therapeutic target for the LDL-C level. Based on this time subanalysis, it is definitely important to preserve an LDL-C level of < 80 mg/dL or < 70 mg/dL for slowing the progression or induction of regression of atherosclerosis.

The results of our subanalysis are consistent with previous reports. O'Leary, *et al*[17] divided more than 5800 elderly patients into 5 subgroups by quintiles of the measured carotid IMT values and followed them for 7 years. They found the relative risk of myocardial infarction or stroke increased for the quintile with the highest thickness compared with the lowest thickness quintile, and the mortality also increased depending on the carotid IMT thickness. von Birgelen, *et al*[7] performed a

meta-analysis of large-scale clinical trials for patients with CAD treated by statins, and reported that there was a positive linear correlation between LDL-C and annual change in plaque size, with an LDL-C value of 75 mg/dL predicting, on average, no plaque progression. Amarenco, *et al*[2] reported that statin treatment was able to reduce the incidence of all strokes without any increase in hemorrhagic strokes, and that this effect was mainly driven by the extent of between-group LDL-C reduction. Carotid IMT progression was also strongly correlated with LDL-C reduction.

On the other hand, ADRs are of concern because of the hypocholesterolemia induced by intensive lipid-lowering therapy using statin medications for low-risk patients. However, no clinically significant differences in safety were observed among the subgroups divided by the LDL-C level at 12 months. Even in the other subgroup with LDL-C < 70 mg/dL, no clinically significant ADRs were observed. Therefore, intensive lipid-lowering therapy may not affect the safety of patients.

In summary, we conducted this subanalysis using subjects from the previously reported JART Study. Even for prevention in Japanese patients, lowering the LDL-C level to below the therapeutic target prevented mean-IMT progression after 12 months more strongly. The findings suggest the need for intensive lipid-lowering therapy from the early stage of dyslipidemia.

Because of a limited amount of data, data pooled from the rosuvastatin and pravastatin groups were used for this analysis. Therefore, differences in drug effects were not taken into account with respect to the progression/regression of atherosclerosis. Because of early termination of the main trial, the statistical power of the analyses to detect the effects on progression/regression of atherosclerosis would be decreased. The treatment effects of longer term therapy should be assessed in a future clinical trial.

Conclusions: We conducted a subanalysis using Japanese patients with hyper-LDL-C who had an IMT of ≥ 1.1 mm measured by carotid artery ultrasound in the previously reported JART Study to determine the relationship between LDL-C and carotid mean-IMT change. Our subanalysis successfully revealed the relationship between the therapeutic target for LDL-C and the mean-IMT change, and therefore, even for prevention in Japanese patients who are at lower-risk than Western patients, lowering the LDL-C level to below the therapeutic target reduced or prevented the mean-IMT progression after 12 months more strongly without any safety concerns.

Appendix

The following persons participated in this trial.

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Effect of Long-Term Intensive Lipid-Lowering Therapy With Rosuvastatin on Progression of Carotid Intima-Media Thickness

– Justification for Atherosclerosis Regression Treatment (JART) Extension Study –

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for the Justification for Atherosclerosis Regression Treatment (JART) Investigators

Background: Recently, it was reported from the Justification for Atherosclerosis Regression Treatment (JART) Study that intensive therapy with rosuvastatin significantly slowed progression of carotid intima-media thickness (IMT) compared with conventional therapy with pravastatin at 12 months. To assess the long-term efficacy of intensive therapy, the present extension study was conducted.

Methods and Results: Subjects in the intensive therapy group of the JART Study were asked to participate in the extension study and to continue rosuvastatin treatment. A total of 113 subjects were enrolled into the extension study and were included in the analysis. At 24 months, the mean daily dose of rosuvastatin (±SD) was 7.9±2.9 mg. Mean change in mean IMT was –0.005 mm (range, –0.024 to 0.015 mm) at 24 months (P=0.633, compared with baseline). Rosuvastatin lowered low-density lipoprotein cholesterol (mean±SD) by 46.4±13.8% and elevated high-density lipoprotein cholesterol (mean±SD) by 8.9±24.0% at 24 months compared with baseline. Gray scale median was measured in 25 subjects. It increased by 16.93±33.12 (mean±SD) % at 12 months and by 22.50±52.83% at 24 months from baseline (P=0.017, P=0.044, respectively).

Conclusions: Two-year treatment with rosuvastatin inhibited progression of carotid IMT. Rosuvastatin also improved the plaque composition, and this qualitative change occurred relatively early after starting therapy.

Key Words: Carotid intima-media thickness; Clinical trial; Dyslipidemia; Hydroxymethylglutaryl-CoA reductase inhibitors; Rosuvastatin

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Continuous accumulation of atherosclerotic plaque is one of the major risk factors for cardiovascular disease. Previous studies using intravascular ultrasound (IVUS) have shown the effects of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) on progression of atherosclerosis.[1–6] These imaging studies also enabled quantitative analysis to investigate the relationship between changes in serum lipids and atheroma volume. A recent meta-analysis using data from imaging studies has shown that regression of atheroma volume can occur when the substantial reduction in low-density lipoprotein cholesterol (LDL-C) is accompanied by an increase in high-density lipoprotein cholesterol (HDL-C).[7] These studies, however, generally included patients who required coronary angiography. Therefore, they were mainly secondary prevention patients.

Carotid artery intima-media thickness (IMT) is a reliable surrogate marker for cardiovascular events.[8–12] O'Leary et al showed that increases in carotid IMT are directly associated with an increased risk of cardiovascular events.[9] It is an intermediate phenotype for early atherosclerosis and can be measured relatively simply and non-invasively on B-mode ultrasound.[10] For these reasons, it has been increasingly used as an endpoint in clinical trials. For example, a recent randomized controlled trial has shown that rosuvastatin slowed progression of maximum carotid IMT in middle-aged individuals with modest carotid IMT thickening.[13] In addition, mean IMT has provided advantages in predicting the risk for cardiovascular events. Mean IMT is obtained by averaging 60 points of IMT at the carotid artery, using Intimascope®. This computer-automated IMT measurement is considered to be more reliable than the established 3-point method.[14]

On the basis of these findings, we designed the Justification for Atherosclerosis Regression Treatment (JART) Study to determine whether intensive lipid-lowering therapy with rosuvastatin is more effective than conventional therapy with pravastatin in slowing atherosclerotic progression by measuring mean IMT.[15] This was a randomized controlled study with a planned follow-up period of 24 months and was stopped according to the recommendation of the data and safety monitoring committee, which reviewed the results of the interim 12-month analysis. It was found that intensive therapy significantly slowed progression of carotid IMT compared with conventional therapy in Japanese subjects,[16] but we could not determine whether intensive therapy further reduces the plaque volume in the longer term because the study was stopped at 12 months.

Accordingly, we conducted the JART Extension Study to assess the long-term effect of intensive lipid-lowering therapy on progression of carotid IMT. The risk of rupture of an atherosclerotic plaque is not only dependent on the plaque size but on the composition of the plaque.[17] Vulnerable plaque is typically characterized by a thin fibrous cap and increased accumulation of lipids and inflammatory cells.[17] This plaque morphology can be assessed as gray scale median (GSM). Thus, we also explored the effects of long-term intensive lipid-lowering therapy on GSM.

Methods

The design and results of the JART Study have been reported previously.[15,16]

Study Design and Ethics Considerations

The JART studies consisted of a prospective, randomized, open-label, blinded-endpoint study and a subsequent open-label extension study. In the randomized study, subjects were assigned to receive rosuvastatin (intensive therapy) or pravastatin (conventional therapy). After the randomized study was stopped, subjects in the intensive therapy group were asked to participate in the extension study and to continue the treatment with rosuvastatin. Patients in the conventional therapy group did not participate in the extension study. Both studies were conducted in accordance with the Declaration of Helsinki and the ethical principles for clinical studies in Japan. Their protocols were reviewed and approved by the institutional review board of each participating center. All subjects provided written informed consent.

Eligibility Criteria

In this study, subjects aged ≥20 years were eligible if they had elevated LDL-C (≥140 mg/dl) and maximum IMT ≥1.1 mm measured at the carotid artery. Serum LDL-C was measured on direct homogeneous assay. Otherwise, serum LDL-C was calculated from the following Friedewald formula.[18]

$$\text{LDL-C} = \text{total cholesterol} - \text{HDL-C} - (\text{triglyceride [TG]}/5)$$

Subjects were excluded if they required lipid-lowering agents other than pre-specified ones (ie, anion-exchange resin, probucol, and ethyl icosapentate); had received statin therapy within 1 month before starting the randomized study; had suspected severe carotid artery stenosis or severe calcification; had familial hypercholesterolemia or secondary hypercholesterolemia; had fasting serum TG ≥400 mg/dl; had a history of hypersensitivity to statins; had uncontrolled hypertension; had type 1 diabetes or uncontrolled type 2 diabetes; experienced myocardial infarction or stroke within 3 months; had severe congestive heart failure, active hepatic disease, renal disorder, or creatine kinase (CK) >500 IU/L. Pregnant women, breast-feeding women, or women who were potentially pregnant during the study were also excluded.

Treatment

In the randomized study, subjects in the intensive therapy group received rosuvastatin 5 mg/day as a starting dose. The daily dose of rosuvastatin was increased to 10 mg if the subject did not achieve the following LDL-C goal: <80 mg/dl for primary prevention and <70 mg/dl for secondary prevention. If the subject did not achieve the LDL-C goal after the dose of rosuvastatin was increased, pre-specified lipid-lowering agents were added thereafter. In the extension study, the dose of rosuvastatin was increased and other agents were added in the same manner.

Outcome Measures

Medical histories were obtained from all subjects before enrollment of the randomized study. Laboratory data including serum lipids were obtained at baseline. Follow-up visits were scheduled at 1, 2, 4, 6, 12, 18, and 24 months throughout the randomized and extension studies. At each visit, serum lipids were measured and treatment compliance was investigated. Laboratory tests were performed at 1, 4, 6, 12, and 24 months. Laboratory data were analyzed at the central laboratory. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at 0 (baseline), 12, and 24 months.

Subjects were scheduled to undergo ultrasonography at 0 (within 3 months before enrollment), 12, and 24 months. B-mode images were obtained according to the guidelines for ultrasonic assessment of carotid artery disease.[19] For the measurement of carotid IMT, 2 longitudinal images were obtained in the 3-cm segment proximal to the tip of the flow divider of the right and left common carotid arteries. The outcome was

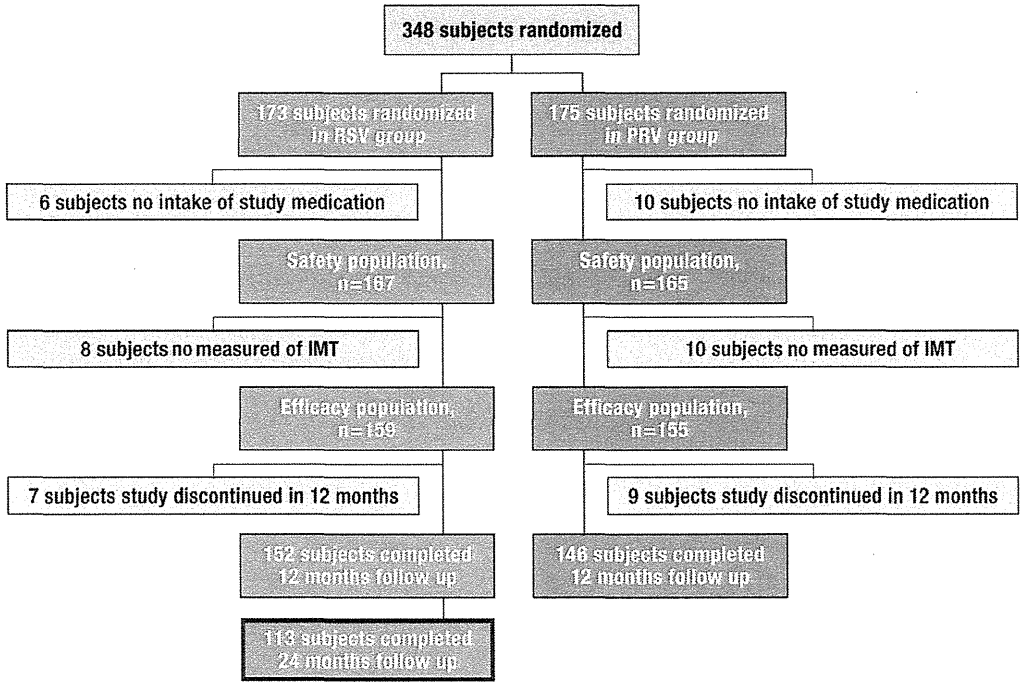

Figure 1. Flow chart of the Justification for Atherosclerosis Regression Treatment and extension studies. IMT, intima-media thickness; PRV, pravastatin; RSV, rosuvastatin.

measured at the far wall of the common carotid artery in which the eligibility criterion of maximum IMT ≥1.1 mm was confirmed. Mean IMT was measured in the core laboratory using Intimascope® (Media Cross, Tokyo, Japan).[14] It averaged 60 points of IMT in the segment 2 cm proximal to the dilation of the carotid bulb. GSM was measured with the method described by Elatrozy et al.[20] For the measurement of GSM, a single experienced technician who was blinded to the subject profile and IMT analyzed the images. GSM was measured in subjects who had baseline mean IMT ≥1.0 mm. The image is obtained under the condition of clear difference between blood area and intima area on the standardization using black. Outlines of an area of plaque, blood, and brightest adventitia at the level of the plaque were drawn in the segment 2 cm proximal to the dilation of the carotid bulb on the B-mode image. The gray scale value of each pixel in the outlined region (0–255; 0, black; 255, white) was used to calculate the GSM. Measurement of GSM was done using Dipp-Image® (DITECT, Tokyo, Japan).

The primary endpoint was the change in mean IMT from baseline to the end of 24 months. The secondary endpoints included GSM, serum lipids, and LDL-C/HDL-C ratio.

Statistical Analysis

The demographic and baseline characteristics are summarized descriptively. In the efficacy analysis, the changes in outcomes from baseline to 12 and 24 months were assessed using paired t-test. In the safety analysis, the frequency and percentage of each adverse drug reaction were summarized descriptively. All data were analyzed using SAS® System Release 9.2 (SAS Institute, Cary, NC, USA). All reported P-values are 2-sided without adjustments for multiple testing.

Results

Trial Profile and Subjects

Figure 1 shows the flow chart of the study. In the rosuvastatin group of the randomized study, 152 subjects completed follow-up during 12 months. Of these, 39 subjects did not participate in the extension study and 113 were included in the final analysis at 24 months.

Table 1 lists the subject demographic and baseline characteristics. Important characteristics were similar to those in the randomized study. Nearly half of the subjects were classified into category III (primary prevention high-risk group) according to the Japan Atherosclerosis Society guidelines.[21] In addition, >60% of subjects had hypertension and nearly half had diabetes (including impaired glucose tolerance [IGT]). At 24 months, the mean daily dose of rosuvastatin (±SD) was 7.9±2.9 mg. A 75% medication adherence rate was achieved in 98.2% (107 subjects) over the study period.

Carotid IMT

Figure 2 shows the changes in mean IMT at 12 and 24 months. The mean IMT (±SD) was 0.916±0.188 mm at baseline (n=113), 0.928±0.190 mm at 12 months and 0.912±0.170 mm at 24 months. Mean change was 0.012±0.082 mm (95% confidence interval [CI]: −0.004 to 0.027 mm) at 12 months and −0.005±0.104 mm (95% CI: −0.024 to 0.015 mm) at 24 months. These changes were not statistically significant as compared with baseline (P=0.141, P=0.633, respectively). The results were unaffected when adjusted for age and gender.

Table 1. Subject Baseline Characteristics

	Rosuvastatin (n=113)
Male	56 (49.6)
Age (years)	63.9±8.1
Elderly (≤65)	58 (51.3)
Blood pressure (mmHg)	
Systolic	133.8±18.2
Diastolic	76.3±11.5
JASGL2007 category	
I	1 (0.9)
II	36 (31.9)
III	56 (49.6)
Secondary prevention	20 (17.7)
CAD risk factors	
Family history of premature CAD	23 (20.4)
Smoking	16 (14.2)
Medical history	
Hypertension	78 (69.0)
Diabetes mellitus	51 (45.1)
Low HDL-C	9 (8.0)
Cerebral infarction	7 (6.2)
Peripheral arterial disease	4 (3.5)
CAD	20 (17.7)
Mean daily dose at 24 months (mg)	7.9±2.9
Other medications	
Anti-hypertensive	68 (60.2)
Anti-diabetic	27 (23.9)
LDL-C (mg/dl)†,‡	164.8±34.1
Max-IMT (mm)	1.48±0.51
HbA_{1c} (NGSP) (%)§	6.27±0.84

Data given as mean±SD or n (%).
†Friedewald formula, LDL-C=total cholesterol–HDL-C–(TG/5).
‡n=111, because of missing measurements. §n=109, because of missing measurements.
CAD, coronary artery disease; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; JASGL, Japan Atherosclerosis Society Guidelines; LDL-C, low-density lipoprotein cholesterol; NGSP, National Glycohemoglobin Standardization Program; TG, triglyceride.

Mean IMT had decreased in 49 subjects (43.4%) at 12 months and in 54 subjects (47.8%) at 24 months.

GSM

GSM was measured in 25 subjects who had baseline mean IMT ≥1.0 mm. As compared with baseline, GSM (mean±SD) increased by 16.93±33.12% (P=0.017) at 12 months and by 22.50±52.83% (P=0.044) at 24 months, whereas mean IMT decreased by 1.36±9.42% (P=0.478) and by 5.16±10.26% (P=0.019) in the same subjects, respectively. **Figure 3** shows the relationship between the changes in GSM and mean IMT in subjects with both measurements. GSM significantly increased at 12 months (P=0.017, compared with baseline) and at 24 months (P=0.044, compared with baseline), but the change in GSM between 12 and 24 months was not statistically significant (P=0.564). In contrast, the change in mean IMT between baseline and 12 months was not statistically significant (P=0.478), whereas a significant decrease in mean IMT occurred at 24 months (P=0.019, compared with baseline).

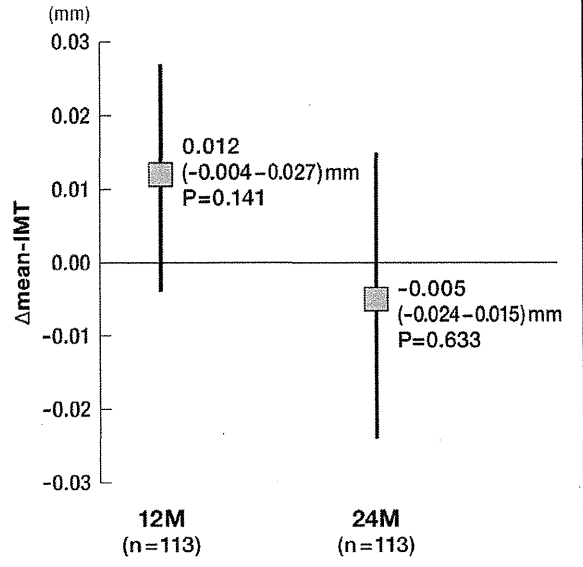

Figure 2. Changes in intima-media thickness (IMT) during treatment with rosuvastatin at 12 and 24 months. Data given as mean (95% confidence interval). P-value was calculated using paired t-test.

Serum Lipids and Other Laboratory Variables

Table 2 lists the changes in serum lipids and LDL-C/HDL-C ratio. Rosuvastatin significantly improved mean serum lipid levels and LDL-C/HDL-C ratio. It lowered LDL-C (mean± SD) by 46.4±13.8%; the mean LDL-C decreased from 164.8± 34.1 mg/dl at baseline to 86.5±19.7 mg/dl at 24 months. It also elevated HDL-C (mean±SD) by 8.9±24.0%. According to these favorable changes in LDL-C and HDL-C, the mean LDL-C/HDL-C ratio (±SD) decreased to 1.6±0.5 at 24 months with the percent reduction of 49.3±13.8%. In addition, rosuvastatin improved the lipid management. At 24 months, 104 subjects (92.0%) achieved the LDL-C goal recommended by the Japan Atherosclerosis Society guidelines. At the same time point, 54 subjects (51.4%) achieved LDL-C/HDL-C ratio ≤1.5, whereas 85 subjects (81.0%) achieved LDL-C/HDL-C ratio ≤2.0.

The mean HbA_{1c} (±SD) was 6.3±0.8% at baseline and 6.5±0.9% at 24 months. The mean SBP/DBP (±SD) was 133.8±18.1/76.3±11.5 mmHg and 129.9±15.1/74.2±10.0 mmHg, respectively. Simple linear regression analysis did not show any meaningful relationship between the changes in blood pressures and HbA_{1c}, and mean IMT (data not shown).

Safety

During the follow-up, 1 subject had a cerebrovascular event.

Table 3 lists the adverse drug reactions during follow-up. Adverse drug reactions occurred in 12 subjects (10.6%), but no serious events were reported. Arthralgia, back pain, and myalgia occurred in 3, 1, and 2 subjects, respectively. One subject experienced IGT. The common laboratory changes were those of liver enzymes. Alanine aminotransferase (ALT) increased in 2 subjects, and aspartate aminotransferase (AST) increased in 1 subject. In addition, CK increased in 2 subjects. No subjects discontinued rosuvastatin due to adverse drug reactions (laboratory IGT was defined by each institution, and increases in ALT, AST, and CK were defined as a 3-fold increase of upper limits of normal at each institution).

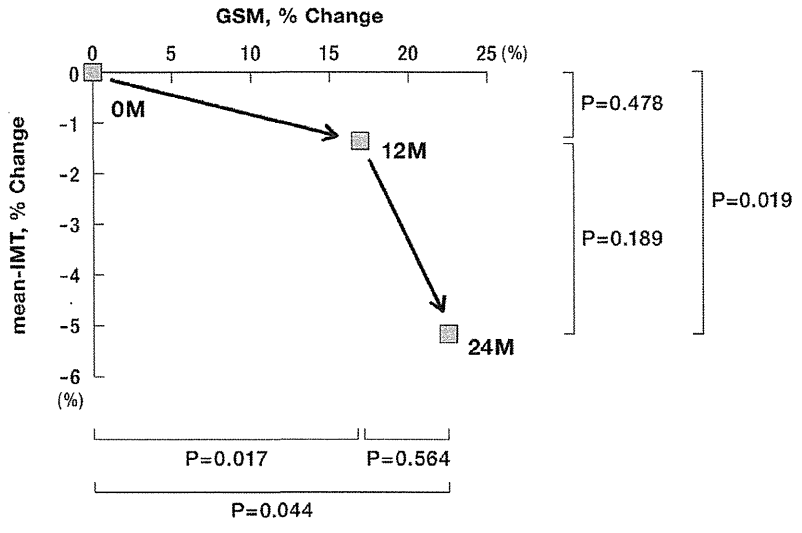

Figure 3. The relationship between the percent changes in gray scale median (GSM) and mean intima-media thickness (IMT) at 12 and 24 months in subjects (n=25) with baseline mean IMT ≥1.0 mm. P-value was calculated using paired t-test.

Table 2. Changes in Serum Lipids at 12, 24 Months

		Change (%)	P-value†
LDL-C‡ (mg/dl)			
Baseline	164.8±34.1 (111)		
12 months	82.7±21.1 (112)	−48.2±16.9 (111)	<0.0001
24 months	86.5±19.7 (105)	−46.4±13.8 (104)	<0.0001
HDL-C (mg/dl)			
Baseline	53.8±11.9 (112)		
12 months	58.2±13.6 (112)	9.3±17.9 (112)	<0.0001
24 months	57.1±14.3 (106)	8.9±24.0 (106)	0.0002
LDL-C‡/HDL-C ratio			
Baseline	3.2±0.9 (111)		
12 months	1.5±0.5 (112)	−51.6±17.2 (111)	<0.0001
24 months	1.6±0.5 (105)	−49.3±13.8 (104)	<0.0001
Non-HDL-C (mg/dl)			
Baseline	194.7±35.0 (112)		
12 months	106.2±22.5 (112)	−44.3±13.7 (112)	<0.0001
24 months	110.4±21.6 (106)	−42.3±13.1 (106)	<0.0001
TG (mg/dl)			
Baseline	153.9±85.8 (112)		
12 months	117.5±54.3 (112)	−13.9±39.4 (112)	0.0003
24 months	122.0±73.6 (106)	−13.4±44.8 (106)	0.0026

Data given as mean±SD (n). †Paired t-test. ‡Friedewald formula, LDL-C=total cholesterol−HDL-C−(TG/5). Abbreviations as in Table 1.

Discussion

We previously reported that 1-year intensive lipid-lowering treatment with rosuvastatin was more effective in slowing progression of carotid IMT than conventional lipid-lowering treatment with pravastatin in the JART Study.[16]

The change in mean IMT in the rosuvastatin group at 12 months was similar to the annual increase of 0.01–0.015 mm in the common carotid artery IMT associated with aging.[19] This indicates that rosuvastatin may halt atherosclerotic progression caused by factors other than aging. In the present study, 2-year treatment with rosuvastatin might induce regression of carotid IMT with regard to progression of carotid IMT with aging. Although not statistically significant, the mean change in mean IMT was <0 mm at 24 months. In addition, the change in mean IMT at 12 months in the extension group (0.012±0.082 mm; 95% CI, −0.004 to 0.027 mm; n=113) was similar to the result in the JART rosuvastatin group at 12 months (0.012±0.093 mm; 95% CI, −0.003 to 0.027 mm; n=145). To consider the clinical meaning of these studies, we summarized the change of mean IMT using the data of the rosuvastatin group in the JART Study at 12 months and the extension group at 24 months. Because carotid IMT is a reliable predictor of cardiovascular events,[8–12] the present finding

Table 3. Adverse Drug Reactions During Follow-up

	Rosuvastatin (n=113)
Serious	0 (0)
Not serious	12 (10.6)
Infections and infestations	
Cystitis	1 (0.9)
Metabolism and nutrition	
IGT†	1 (0.9)
Nerve	
Headache	1 (0.9)
Gastrointestinal	
Abdominal discomfort	2 (1.8)
Nausea	1 (0.9)
Hepatobiliary	
Liver function abnormality	1 (0.9)
Skin and subcutaneous tissue	
Eczema	1 (0.9)
Generalized rash	1 (0.9)
Pruritic rash	1 (0.9)
Musculoskeletal and connective tissue	
Arthralgia	3 (2.7)
Back pain	1 (0.9)
Myalgia	2 (1.8)
Heaviness	2 (1.8)
Musculoskeletal stiffness	1 (0.9)
Kidney	
Hematuria	1 (0.9)
General disorders and injection site conditions	
Ineffectiveness	2 (1.8)
Discomfort	1 (0.9)
Malaise	2 (1.8)
Peripheral edema	1 (0.9)
Laboratory tests	
ALT increased‡	2 (1.8)
AST increased‡	1 (0.9)
CK increased‡	2 (1.8)
GGT increased	1 (0.9)

Data given as n (%).
†As defined by each institution. ‡Defined as 3-fold increase of upper limits of normal in each institution.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; GGT, γ-glutamyltransferase; IGT, impaired glucose tolerance.

supports "the longer, the better" hypothesis, whereas that of the randomized study supports "the lower, the better" hypothesis in Japanese subjects.

Effects of statins on progression of atherosclerosis have been well established. In A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID), 2-year treatment with rosuvastatin 40 mg resulted in regression of coronary atherosclerosis.[2] In the Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects (COSMOS), a mean daily dose of 16.9 mg rosuvastatin induced regression of coronary plaque volume at the end of 76-week follow-up.[3] Furthermore, in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN), maximum doses of rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis after 2 years of treatment.[22] These studies, however, included secondary prevention patients, who are generally at the highest risk for cardiovascular events. In contrast, the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial included low-risk individuals with mild atherosclerosis and showed that 2-year treatment with rosuvastatin 40 mg did not result in significant regression of atherosclerosis although it significantly slowed progression.[13] The present result suggests that long-term intensive therapy would be expected to induce atherosclerotic regression in Japanese subjects, who are at relatively low risk for cardiovascular events.

The beneficial effect of intensive therapy on plaque volume was mainly derived from modulation of serum lipid levels. In the present study, rosuvastatin lowered mean LDL-C to 86.5 mg/dl at a mean daily dose of 7.9 mg. This indicates that intensive therapy to lower LDL-C to 80 mg/dl is beneficial in Japanese subjects. In addition, rosuvastatin elevated HDL-C by 8.9% and decreased mean LDL-C/HDL-C ratio to 1.6. In a recent meta-analysis, reduction of LDL-C to <87.5 mg/dl provided coronary atherosclerotic regression when accompanied by an approximately 7.5% increase in HDL-C.[7] That meta-analysis has also shown that LDL-C/HDL-C ratio should be managed to <1.5 to decrease atheroma volume. The present results are consistent with those of the meta-analysis and indicate the importance of managing LDL-C/HDL-C ratio in the long term.

Recently, Lorenz et al reported a meta-analysis on the association between cardiovascular risk and change of carotid IMT.[23] They considered, however, only the quantity of plaque; it may be important to take into account the quality in addition to the quantity. Soeda et al reported that lipid-lowering therapy with statins may reduce plaque volume and stabilize vulnerable plaque.[24] We also explored the relationship between changes in composition and volume of plaque. We found that a significant increase in GSM occurred at 12 months followed by a significant decrease in mean IMT at 24 months. Echogenic plaque has a more stable phenotype and is associated with lower risk for cardiovascular events, whereas echolucent plaque contains more lipid and less fibrous tissue.[25–27] Thus, the present results suggest that a qualitative change in plaque may occur relatively early after starting intensive therapy, followed by a quantitative change. A previous study using angioscopy and IVUS has shown similar results.[28] In that study, subjects with coronary artery disease were treated with atorvastatin, and serial analysis showed early loss of yellow color in plaque and subsequent plaque regression. Because the reduction in yellow color intensity is attributable to a change in the thickness of the fibrous cap, these changes suggested that the improvement in plaque characteristics occurs early, whereas the reduction in atheroma volume occurs over a prolonged period.[28] The beneficial effect of statin on the thickness of the fibrous cap was also reported in a study using intravascular optical coherence tomography.[29]

Rosuvastatin was well-tolerated during the 2-year follow-up. No serious adverse drug reaction was reported. Relatively few patients experienced myopathy or hepatotoxicity – the most clinically important adverse reactions of statins – such as muscle symptoms, and increases in CK, ALT, or AST. In the analysis of other laboratory variables, mean HbA_{1c} increased and mean SBP and DBP decreased during treatment, but these changes were thought not to be clinically meaningful. Although IGT occurred in only 1 subject, the changes in HbA_{1c}, SBP and DBP did not affect progression of carotid IMT.

Study Limitations

Some limitations should be mentioned. First, we adopted an open-label design, which might induce bias in assessing the outcomes. Although mean IMT was measured using computer software, the observer knew whether the datum was obtained at baseline or follow-up. Second, we did not enroll subjects in the conventional therapy group of the JART Study. Thus, the sample size was too small to obtain statistically significant changes in the primary endpoint. The JART Study was initially planned to continue for 24 months, but was stopped at 12 months on the recommendation of the safety and monitoring committee. The JART Extension Study was then conducted to assess the long-term efficacy of intensive lipid-lowering therapy in the rosuvastatin group in the JART Study. This placed an inherent limitation on the sample size, but although this sample size does not provide sufficient power for statistical significance, we feel that the trend identified in this study will be of interest because of the large number of patients potentially affected. Third, GSM was evaluated in a limited number of subjects. This led to a reduction of statistical power to detect the treatment effect on GSM.

Conclusions

First, long-term intensive lipid-lowering therapy with rosuvastatin inhibited progression of carotid IMT and improved the plaque composition in Japanese subjects. Second, qualitative change in plaque may occur relatively early after starting intensive therapy. We also found that long-term intensive therapy was well-tolerated. Further study is warranted to confirm the effects of long-term intensive therapy on the quality and quantity of atherosclerotic plaque in Japanese subjects.

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The other authors have no conflicts of interest.

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Appendix 1

The following persons participated in this trial.

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Original article

Prognostic impact of chronic kidney disease on 10-year clinical outcomes among patients with acute coronary syndrome

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ABSTRACT

Background: Chronic kidney disease (CKD) is closely associated with a higher risk of cardiovascular disease. However, whether patients with acute coronary syndrome (ACS) and CKD are at increased risk for long-term mortality after coronary revascularization remains unknown.
Methods and results: Data from consecutive patients with ACS who had undergone coronary revascularization, including percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) were analyzed. The estimated glomerular filtration rate (eGFR) was calculated using the current Japanese equation and CKD was defined as eGFR < 60 mL/min/1.73 m^2. Among 375 enrolled patients with ACS, 75 (20.0%) had CKD. During a follow-up period of 10.0 ± 3.4 years, the total number of deaths was 80 (21.3%), of which 36 (9.6%) were due to cardiovascular causes. Kaplan–Meier analysis showed that the presence of CKD was associated with a significant increase in mortality from all causes (log-rank test, $p < 0.001$) and cardiovascular mortality ($p < 0.001$). Cox proportional-hazard analysis revealed that CKD increased the risk of mortality with a hazard ratio of 2.31 (95% confidence interval (CI): 1.25–4.29, $p = 0.008$) and of cardiovascular death with a hazard ratio of 3.76 (95% CI: 1.60–8.80, $p = 0.002$) in patients with ACS.
Conclusions: CKD is a powerful determinant of long-term all-cause and cardiovascular mortality after ACS.

1. Introduction

Chronic kidney disease (CKD) is a prevalent and widespread disease that might be a focus of not only patients, but also of physicians and of the healthcare system. CKD is closely associated with a higher risk of cardiovascular disease (CVD), and the presence of CKD is a potent predictor of a worse prognosis among patients with coronary artery disease [1–6]. Coronary revascularization therapy including percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) is being applied to a widening spectrum of patients, including those with CKD [7–10]. In addition, patients with acute coronary syndrome (ACS) have higher mortality than patients with stable angina and prognosis of ACS remains poor despite therapeutic advances including coronary revascularization [11]. Accordingly, it is important to identify factors that might contribute to the poor prognosis in patients with ACS. Although several studies have shown a harmful effect of CKD on short-term clinical outcomes after coronary revascularization therapy [3,12], whether patients with ACS and CKD are at increased long-term (>10 years) risk for cardiovascular events after coronary revascularization therapy has not been determined. Moreover, the association between CKD based on glomerular filtration rates (GFRs) estimated using the current Japanese equation and long-term prognosis has not yet been defined [13]. Therefore, we investigated the significance of CKD on >10-year clinical outcomes of patients with ACS who were treated with coronary revascularization therapy.

2. Methods

2.1. Patients and data collection

This study is a retrospective analysis of prospectively gathered data. The data from 375 consecutive patients who had undergone coronary revascularization, including percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) at

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Juntendo University Hospital (Tokyo, Japan) between January 1984 and December 1992 were analyzed. We enrolled patients with ACS who had undergone complete revascularization, defined as the absence of bypassed major vessels with ≥50% stenosis, to minimize the influence of adverse outcomes related to incomplete procedures [14,15]. We identified ACS among patients with acute myocardial infarction (MI) and unstable angina. Acute MI was diagnosed based on the presence of typical chest pain with ST-segment elevation on electrocardiograms or increased serum creatine kinase levels. Unstable angina was diagnosed based on the presence of characteristic chest pain symptoms at rest associated with transient ischemic ST-segment shifts and normal serum creatine kinase levels.

Patients on dialysis were excluded to identify the mortality risk associated with CKD independently of dialysis. Patients with an untreated neoplasm at baseline and those with associated complex cardiac procedures such as valve replacement or aneurysm repair at the time of surgical revascularization, as well as those who were not Japanese were also excluded. Demographic data, including age, gender, body mass index (BMI), coronary risk factors, medication use, revascularization procedure-related factors, and comorbidities were collected from our institutional database.

Estimated GFR (eGFR) was obtained by using the following specific equation for Japanese: $GFR = 194 \times [sCr]^{-1.094} \times [Age]^{-0.287}$ ($\times 0.739$ if female) [13]. We defined CKD as an eGFR < 60 mL/min/1.73 m^2. This value is the generally accepted cutoff value for CKD and corresponds to CKD stages 3–5, according to the National Kidney Foundation practice guidelines [16]. Patients with eGFR ≥60 mL/min/1.73 m^2 were not placed in the group without CKD because some of them might have had chronic kidney damage for ≥3 months despite having a higher eGFR. Therefore, patients were assigned to a group with a preserved eGFR that included patients with eGFR ≥60 mL/min/1.73 m^2, or a group with CKD, which included patients with eGFR < 60 mL/min/1.73 m^2.

Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or treatment with antihypertensive medication. Diabetes mellitus (DM) was defined as a fasting plasma glucose level ≥126 mg/dL or being under treatment with oral hypoglycemic drugs or insulin injections. A current smoker was defined as a person who smoked at the time of complete revascularization or who had quit smoking within one year before complete revascularization. Patients with isolated PCI were those in whom complete revascularization was achieved by PCI without the need for bypass grafting.

Outcome data were collected by serial contact (every 5 years) with the patients or their families until September 2000. The medical records of patients who died or who were treated at our hospital were analyzed. We collected data for subjects who discontinued to be followed up at our institution by mailing or by telephone. Then, information about the circumstances and date of death was obtained from the families of subjects who died at home, and details of the cardiac events or the cause of death were supplied by other hospitals or clinics where patients had been admitted. Mortality data were categorized as death from all causes or cardiovascular death including death from coronary artery disease, stroke, cardiogenic shock, and sudden death.

This study was approved by the internal review board of Juntendo University hospital, and proceeded according to the principles expressed in the Declaration of Helsinki and the ethics policy of this institute.

2.2. Statistical analysis

Continuous variables are expressed as means ± SD. Normally distributed variables were compared using Student's *t*-test, and the Mann–Whitney *U* test was used for non-parametric analyses. Categorical data were tabulated as frequencies and ratios, and were compared using the Chi-square test or the Fisher exact test.

Survival was compared between patients in the groups with CKD and with preserved eGFR using the Kaplan–Meier estimate with the log-rank test. Hazard ratios (HRs) of the CKD group were calculated using the Cox proportional hazards model. The assumption of proportional hazards was assessed using a log-minus-log survival plot. Univariable analysis was based on the proportional hazards model to determine the association between both all-cause and cardiovascular deaths and the following variables: age, gender, BMI, current smoker, DM, hypertension, total and high density lipoprotein (HDL) cholesterol, triglyceride, hemoglobin, serum creatinine, atrial fibrillation, prior MI, prior stroke, left ventricular ejection fraction (LVEF), multivessel disease, use of an arterial bypass graft, whether complete revascularization was achieved by isolated PCI, use of drugs, and the CKD group or the preserved eGFR group. Variables regarded as significant (i.e. $p \leq 0.10$) were included in the multivariable analysis. Multivariable analyses verified the interactions between each variable.

A *p*-value of <0.05 was considered statistically significant, unless otherwise indicated. All data were analyzed using SPSS version 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics and prevalence of factors

Among the 375 patients with ACS, 75 (20%) had CKD. In the present study, 186 (49.6%) subjects underwent complete revascularization with plain old balloon angioplasty and 189 (50.4%) with CABG. Baseline and clinical event data were fully documented during the follow-up period (mean 10.0 ± 3.4 years) for all of these patients (Table 1). Patients with CKD were older and more likely

Table 1
Baseline characteristics.

	Preserved eGFR $N=300$	CKD $N=75$	*p*-Value
Age (years)	59.4 ± 8.8	63.6 ± 7.7	<0.001
Male, *n* (%)	228 (76.0)	67 (89.3)	0.018
BMI (kg/m^2)	23.3 ± 2.7	23.3 ± 2.6	0.904
Smoker, *n* (%)	216 (72.0)	60 (80.0)	0.208
Family history of CAD, *n* (%)	91 (30.3)	20 (26.7)	0.631
Diabetes mellitus, *n* (%)	111 (37.0)	33 (44.0)	0.326
Hypertension, *n* (%)	185 (61.7)	45 (60.0)	0.895
Total cholesterol (mg/dL)	218.5 ± 52.6	229.7 ± 46.2	0.090
HDL cholesterol (mg/dL)	43.6 ± 13.4	43.9 ± 12.4	0.864
Triglyceride (mg/dL)	155.2 ± 86.5	176.9 ± 97.6	0.081
Creatinine (mg/dL)	0.70 ± 0.16	1.26 ± 0.52	<0.001
eGFR (mL/min/1.73 m^2)	97.7 ± 36.1	50.5 ± 11.1	<0.001
Hemoglobin (g/dL)	13.4 ± 1.5	13.0 ± 1.8	0.050
Atrial fibrillation, *n* (%)	37 (12.3)	9 (12.0)	1.000
Prior stroke, *n* (%)	8 (2.7)	2 (2.7)	1.000
Prior MI, *n* (%)	91 (30.3)	25 (33.3)	0.717
Multivessel disease, *n* (%)	199 (66.3)	52 (69.3)	0.721
LVEF (%)	64.0 ± 13.1	62.6 ± 13.2	0.407
Revascularization-isolated PCI, *n* (%)	180 (60.0)	43 (56.3)	0.772
Use of arterial bypass graft, *n* (%)	61 (20.3)	9 (12.0)	0.136
Medication			
ACE inhibitors, *n* (%)	16 (5.3)	4 (5.3)	1.000
β-Blocker, *n* (%)	66 (22.0)	23 (30.7)	0.115
Aspirin, *n* (%)	214 (71.3)	55 (73.3)	0.841
Warfarin, *n* (%)	94 (31.3)	22 (29.3)	0.845
Statins, *n* (%)	68 (22.7)	17 (22.7)	1.000

ACE, angiotensin-converting enzyme; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

to be male than those with preserved eGFR. They also had a tendency toward greater cholesterol and triglyceride levels and lower hemoglobin as compared with the group with preserved eGFR. Serum creatinine was greater and eGFR was lower in the CKD group by definition. None of the other characteristics significantly differed between two groups. None of the patients in either group had been implanted with stents since all underwent PCI using balloon angioplasty.

3.2. Univariable and multivariable analysis for all-cause and CV mortality

Cardiovascular mortality accounted for 45% ($n=36$) of the 80 (21.3%) patients who died during long-term follow. Kaplan–Meier analysis showed that the presence of CKD at the time of revascularization was associated with a significant increase in mortality from all causes and cardiovascular mortality (log-rank test: $p<0.001$ for both) (Fig. 1A and B).

Table 2 shows the results of the univariable analysis for all-cause death. Variables that were associated with all-cause death were age, smoking history, serum creatinine level, hemoglobin level, atrial fibrillation, prior MI, multivessel disease, LVEF, and revascularization achieved by isolated PCI in addition to the presence of CKD. Thus, these were included into multivariable analysis, which revealed the presence of CKD is a significant independent risk for all-cause mortality (hazard ratio (HR), 2.31; 95% confidence interval (CI), 1.25–4.29; $p=0.008$) in addition to more advanced age (HR, 1.05; 95%CI, 1.02–1.08; $p=0.002$), presence of atrial fibrillation (HR, 2.24; 95%CI, 1.28–3.90; $p=0.004$), prior MI (HR, 1.95; 95%CI, 1.09–3.47; $p=0.024$), and multivessel disease (HR, 2.34; 95%CI, 1.07–5.14; $p=0.034$).

Table 3 also shows the results of the univariable analysis of cardiovascular death. Variables in addition to the presence of CKD that were associated with cardiovascular death were serum levels of total cholesterol and creatinine, as well as atrial fibrillation, prior MI and stroke, multivessel disease, and LVEF. These factors were included in the multivariable analysis. The findings showed that presence of CKD imposes a significant independent risk for cardiovascular mortality (HR, 3.76; 95%CI, 1.60–8.80; $p=0.002$) in addition to the presence of atrial fibrillation (HR, 3.57; 95%CI, 1.66–7.68; $p=0.001$), and multivessel disease (HR, 3.17; 95%CI, 1.06–9.53; $p=0.039$).

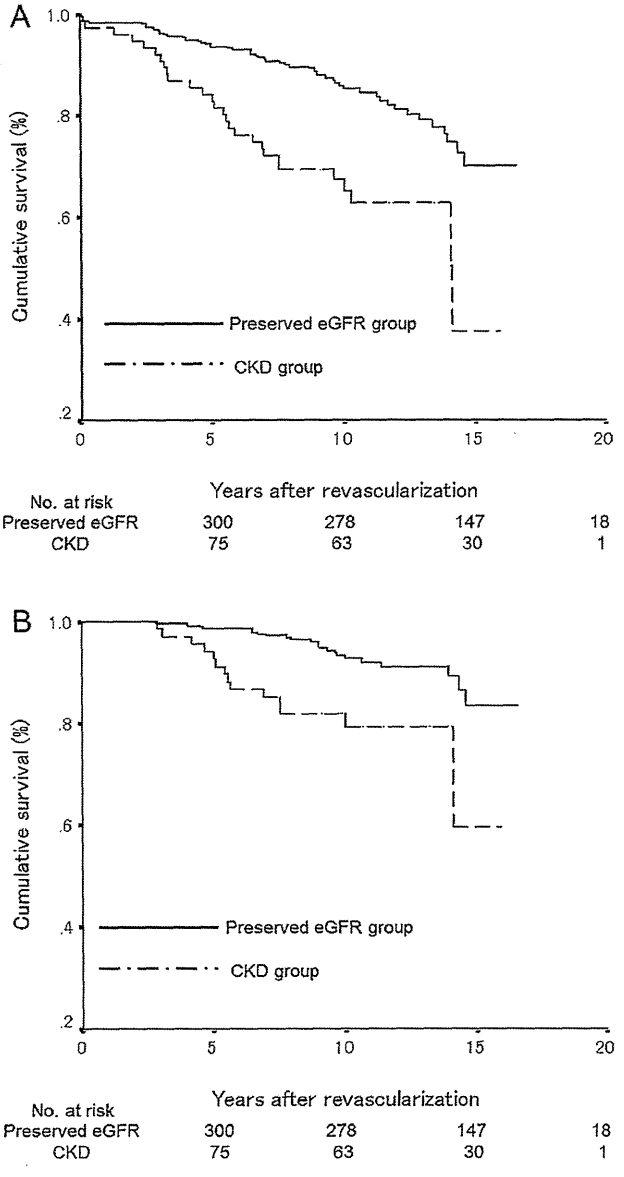

Fig. 1. Results of survival analysis. (A) All-cause death. Cumulative survival rates were significantly lower in patients with chronic kidney disease (CKD) (log-rank test: $p<0.001$) and (B) cardiovascular death: cumulative survival rates were significantly lower in patients with CKD (log rank test: $p<0.001$). eGFR, estimated glomerular filtration rate.

4. Discussion

The present study demonstrated that CKD was significantly associated with the long-term clinical outcomes of ACS patients after complete coronary revascularization. Moreover, even after adjustment for important factors by multivariable Cox regression models, CKD remains a significant predictor of negative long-term clinical outcomes after ACS. Finally, CKD was defined based on eGFR levels using the current equation for Japanese.

Impaired renal function is related to death and cardiovascular events in patients with ACS [17,18]. Several others also have identified CKD as a powerful independent predictor of adverse outcomes after PCI and CABG [3,19–21]. Additionally, studies of long-term outcomes after ACS have revealed a negative effect of CKD on clinical outcomes a few years after revascularization therapy, namely, the follow-up limit of most studies [8,22–24]. Thus, we consider that our results not only confirm the clinical impact of CKD in patients with ACS after coronary revascularization therapy but also show the clinical impact of CKD on long-term outcomes in patients with severe coronary artery disease. Indeed, survival rates for up to 3 years were similar between the groups with preserved eGFR and with CKD, whereas mortality significantly diverged during the later phase (Fig. 1) and was very clear around 10 years. After adjustment for important factors by multivariable Cox regression models, CKD remained a significant predictor of negative long-term clinical outcomes after ACS. Consequently, we believe that our findings clarify the clinical significance of even a moderate degree of impaired renal function over the long term after ACS.

Several factors such as excess comorbidities, underuse of beneficial treatment strategies for secondary prevention, therapeutic toxicity, and abnormal vascular pathology of CKD might contribute to the relationship between CKD and worse outcomes [25]. In addition, coexisting conditions such as diabetes and hypertension, as well as the presence of impaired renal function itself, can lead to activation of the renin-angiotensin system, oxidative stress, elevated asymmetric dimethylarginine, low-grade inflammation with increased circulating cytokines and dyslipidemia, all of which play significant roles in relationships between impaired renal function

Table 2
Risks for all-cause mortality in univariable and multivariable analyses.

	Univariable			Multivariable		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age	1.06	1.03–1.09	<0.001	1.05	1.02–1.08	0.002
Male sex	1.01	0.59–1.72	0.979	–	–	–
BMI	0.95	0.87–1.03	0.182	–	–	–
Hypertension	1.35	0.84–2.15	0.211	–	–	–
Diabetes mellitus	1.44	0.92–2.24	0.109	–	–	–
Total cholesterol	1.00	099–1.01	0.292	–	–	–
Triglyceride	1.00	0.99–1.00	0.611	–	–	–
HDL cholesterol	1.00	0.99–1.02	0.703	–	–	–
Current smoker	0.58	0.37–0.93	0.022	0.67	0.42–1.09	0.109
Family history of CAD	1.30	0.82–2.06	0.272	–	–	–
Serum creatinine	1.80	1.18–2.75	0.006	1.20	0.60–2.41	0.607
CKD	2.64	1.66–4.19	<0.001	2.31	1.25–4.29	0.008
Hemoglobin	0.87	0.76–1.00	0.052	0.96	0.82–1.12	0.580
Atrial fibrillation	2.61	1.54–4.42	<0.001	2.24	1.28–3.90	0.004
Prior MI	2.73	1.76–4.24	<0.001	1.95	1.09–3.47	0.024
Prior stroke	2.04	0.64–6.49	0.228	–	–	–
Multivessel disease	3.50	1.80–6.79	<0.001	2.34	1.07–5.14	0.034
Use of arterial bypass graft	0.72	0.38–1.37	0.321	–	–	–
LVEF	0.97	0.96–0.99	0.001	0.99	0.97–1.00	0.135
Revascularization-isolated PCI	2.24	1.31–3.84	0.003	0.93	0.45–1.93	0.853
Aspirin	0.86	0.54–1.38	0.536	–	–	–
ACE inhibitors	1.43	0.58–3.54	0.442	–	–	–
Beta blockers	1.08	0.65–1.78	0.768	–	–	–
Statins	0.71	0.37–1.35	0.298	–	–	–

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HDL, high density lipoprotein; CAD, coronary artery disease; CKD, chronic kidney disease; MI, myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme.

and cardiovascular events [26]. Furthermore, platelet dysfunction related to CKD and dosing errors of antithrombotic agents can increase bleeding risk among CKD patients and contribute to increased mortality [27]. Hence, we considered that we could confirm that CKD independently affects poor clinical outcomes in patients with ACS over the long term. We also believe that more comprehensive intervention for impaired renal function from the early phase might be needed to improve the worse prognosis associated with CKD. This means that CKD should be recognized and treated in the early phase after an ACS episode or revascularization procedures. A recent retrospective study investigated whether advances in ACS management such as statins, anti-thrombotic agents, and an early invasive approach have improved the prognosis of patients with CKD [8]. One-year cardiovascular event rates increased with decreasing baseline renal function, confirming that the prognosis of these patients remains poor despite contemporary practice including an early invasive approach. A more recent multicenter observational study demonstrated an independent

Table 3
Risks for cardiovascular mortality in univariable and multivariable analyses.

	Univariable			Multivariable		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age	1.03	0.99–1.07	0.214	–	–	–
Male sex	1.36	0.57–3.27	0.491	–	–	–
BMI	1.01	0.89–1.14	0.899	–	–	–
Hypertension	1.68	0.81–3.48	0.165	–	–	–
Diabetes mellitus	1.67	0.87–3.22	0.126	–	–	–
Total cholesterol	1.01	1.00–1.02	0.022	1.01	0.99–1.01	0.097
Triglyceride	1.00	0.99–1.00	0.517	–	–	–
HDL cholesterol	0.99	0.96–1.01	0.305	–	–	–
Current smoker	0.82	0.39–1.69	0.583	–	–	–
Family history of CAD	0.99	0.48–2.05	0.973	–	–	–
Serum creatinine	2.03	1.16–3.58	0.014	0.90	0.95–1.01	0.819
CKD	3.29	1.67–6.48	0.001	3.76	1.60–8.80	0.002
Hemoglobin	0.91	0.74–1.12	0.380	–	–	–
Atrial fibrillation	3.72	1.79–7.74	<0.001	3.57	1.66–7.68	0.001
Prior MI	1.99	1.03–3.84	0.039	1.11	0.53–2.32	0.777
Prior stroke	3.38	0.80–14.2	0.097	1.55	0.34–7.16	0.575
Multivessel disease	4.00	1.41–11.3	0.009	3.17	1.06–9.53	0.039
Use of arterial bypass graft	0.90	0.37–2.18	0.817	–	–	–
LVEF	0.97	0.95–0.99	0.013	0.98	0.95–1.01	0.112
Revascularization-isolated PCI	1.77	0.83–3.80	0.138	–	–	–
Aspirin	1.16	0.56–2.41	0.698	–	–	–
ACE inhibitors	1.28	0.31–5.35	0.738	–	–	–
Beta blockers	1.70	0.86–3.36	0.130	–	–	–
Statins	0.71	0.27–1.86	0.489	–	–	–

ACE, angiotensin-converting enzyme; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; HDL, high density lipoprotein; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

association between in-hospital coronary revascularization and improved one-year survival, irrespective of eGFR [28]. Although these studies observed increased referral rates over consecutive years for in-hospital coronary angiography and revascularization irrespective of renal dysfunction, patients with CKD continue to be treated more conservatively, with an associated worse outcome [28,29]. Therefore, we believe that further prospective studies are needed to define an optimal ACS management strategy from the early phase in patients with CKD.

One limitation of the present study was that the presence of structural kidney disease was not determined in our study participants from findings such as abnormal ultrasound findings or proteinuria. Therefore, we might not have accurately defined and evaluated patients with CKD whose eGFR was >60 mL/min/1.73 m^2. However, we consider that a simple separation determined by eGFR is feasible for routine clinical practice, especially for the secondary prevention of coronary artery disease.

In conclusion, CKD was associated with higher long-term all-cause and cardiovascular mortality after ACS. Moreover, CKD based on eGFR determined using the current Japanese equation was an independent negative predictor of long-term survival even after adjustment for confounding variables. Early recognition and treatment for CKD should be considered as a means of secondary prevention of coronary artery disease after successful coronary revascularization therapy in patients with ACS.

Conflict of interest

The authors have declared that no conflict of interest exists.

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糖尿病合併症発症・進展阻止のための包括的管理

血圧管理

Treatment of hypertension

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Key words：高血圧，糖尿病性腎症，心血管疾患，ACE阻害薬，アンジオテンシンII受容体拮抗薬(ARB)

はじめに

糖尿病が心血管疾患のハイリスクであることは，数多くの報告があり，周知の事実であるが，糖尿病に高血圧が合併すると，心血管疾患の発症率は，2-3倍に増加する[1]．糖尿病患者の50-60％は，最終的に高血圧を合併するといわれており，糖尿病合併症発症・進展阻止のために血圧管理が非常に重要である．

本稿では，糖尿病患者の血圧管理，治療目標，治療指針，更には今後の問題点について概説する．

1 糖尿病合併症と高血圧

糖尿病合併症には，大きく細小血管障害による合併症と大血管障害による合併症がある．細小血管障害による合併症としては，腎症や神経障害，網膜症があり，大血管障害による合併症としては，脳血管障害や虚血性心疾患，閉塞性動脈硬化症があげられる．いずれの合併症も重症化すると患者のQOLは著しく低下し，死に至ることもある．糖尿病も高血圧も大血管障害の危険因子の一つであり，糖尿病と高血圧が合併すると脳血管障害や虚血性心疾患の発症頻度が大きく増加することが報告されている[2]．我が国において，糖尿病患者における高血圧の頻度は，非糖尿病者に比べ約2倍高く[1]，糖尿病患者およびその予備軍が加速度的に増加し，合併症治療のために費やされる医療費も年々上昇してきていることから，血糖管理とともに厳重な血圧管理は重要な課題である．

2 高血圧と心血管病危険因子

高血圧は脳卒中の最も重要な危険因子であるが，高血圧治療ガイドライン(JSH)2009では，高血圧患者の予後は高血圧のほかに，**表1**に示す高血圧以外の危険因子の有無が深く関与することが示されている．確定診断された糖尿病は，独立した強い危険因子であることが示されており，心血管病の危険因子の一つに，我が国の診断基準に基づいたメタボリックシンドロームが新しく追加された．また，**表2**に(診察室)血圧に基づいた脳心血管リスクを層別化したものを示したが，糖尿病はリスク第三層にあてはまり，正常高値血圧でも高リスクとなる．これによると正常高値血圧であっても糖尿病，心血管病，CKDを伴う場合は，積極的な降圧治療の対象となる．

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表1　高血圧管理計画のためのリスク層別化に用いる予後影響因子
（高血圧治療ガイドライン（JSH）2009より引用）

A. 心血管病の危険因子
- 高齢（65歳以上）
- 喫煙
- 収縮期血圧，拡張期血圧レベル
- 脂質異常症
  - 低HDLコレステロール血症（＜40 mg/dL）
  - 高LDLコレステロール血症（≧140 mg/dL）
  - 高トリグリセリド血症（≧150 mg/dL）
- 肥満（BMI≧25）（特に腹部肥満）
- メタボリックシンドローム[*1]
- 若年（50歳未満）発症の心血管病の家族歴
- 糖尿病
  - 空腹時血糖≧126 mg/dL
  - あるいは
  - 負荷後血糖2時間値≧200 mg/dL

B. 臓器障害/心血管病
- 脳　脳出血・脳梗塞
  - 無症候性脳血管障害
  - 一過性脳虚血発作
- 心臓　左室肥大（心電図，心エコー）
  - 狭心症・心筋梗塞・冠動脈再建
  - 心不全
- 腎臓　タンパク尿（尿微量アルブミン排泄を含む）
  - 低いeGFR[*2]（＜60 mL/分/1.73 m²）
  - 慢性腎臓病（CKD）・確立された腎疾患（糖尿病性腎症・腎不全など）
- 血管　動脈硬化性プラーク
  - 頸動脈内膜・中膜壁厚＞1.0 mm
  - 大血管疾患
  - 閉塞性動脈疾患（低い足関節上腕血圧比：ABI＜0.9）
- 眼底　高血圧性網膜症

[*1]メタボリックシンドローム：予防的な観点から以下のように定義する．正常高値以上の血圧レベルと腹部肥満（男性85 cm以上，女性90 cm以上）に加え，血糖値異常（空腹時血糖110–125 mg/dL，かつ/または糖尿病に至らない耐糖能異常），あるいは脂質代謝異常のどちらかを有するもの．

[*2]eGFR（推算糸球体濾過量）は日本人のための推算式，
$eGFR = 194 \times Cr^{-1.094} \times 年齢^{-0.287}$（女性は×0.739）より得る．

表2　（診察室）血圧に基づいた脳心血管リスク層別化
（高血圧治療ガイドライン（JSH）2009より引用）

血圧分類 / リスク層（血圧以外のリスク要因）	正常高値血圧 130–139/85–89 mmHg	I度高血圧 140–159/90–99 mmHg	II度高血圧 160–179/100–109 mmHg	II度高血圧 ≧180/≧110 mmHg
リスク第一層（危険因子がない）	付加リスクなし	低リスク	中等リスク	高リスク
リスク第二層（糖尿病以外の1–2個の危険因子，メタボリックシンドローム*がある）	中等リスク	中等リスク	高リスク	高リスク
リスク第三層（糖尿病，CKD，臓器障害/心血管病，3個以上の危険因子のいずれかがある）	高リスク	高リスク	高リスク	高リスク

*リスク第二層のメタボリックシンドロームは予防的な観点から以下のように定義する．正常高値以上の血圧レベルと腹部肥満（男性85 cm以上，女性90 cm以上）に加え，血糖値異常（空腹時血糖110–125 mg/dL，かつ/または糖尿病に至らない耐糖能異常），あるいは脂質代謝異常のどちらかを有するもの．両者を有する場合はリスク第三層とする．他の危険因子がなく腹部肥満と脂質代謝異常があれば血圧レベル以外の危険因子は2個であり，メタボリックシンドロームとあわせて危険因子3個とは数えない．