Change in Carotid Intima-Media Thickness in a High-Risk Group of Patients by Intensive Lipid-Lowering Therapy With Rosuvastatin

Subanalysis of the JART Study

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Summary

Carotid intima-media thickness (IMT), a measure of atherosclerosis, is modulated by multiple risk factors. Accordingly, comprehensive control of risk factors is indispensable for management of atherosclerosis. In this study, as a post-hoc analysis of the JART Study we planned two analyses. In the main analysis, we evaluated the effect of intensive lipid-lowering therapy with rosuvastatin on carotid IMT in high-risk patients. We also evaluated efficacy in the presence or absence of each risk factor using the full analysis population in the JART Study. Patients with low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL and max-IMT ≥ 1.1 mm were randomized to rosuvastatin or pravastatin therapy for 12 months. Dosages were allowed to increase to 10 mg/day and 20 mg/day to achieve LDL-goals (aggressive goals for rosuvastatin group and guideline goals for pravastatin group). For the main analysis, we assessed 200 high-risk patients (105 in the rosuvastatin group), as category III or secondary prevention according to the Japan Atherosclerosis Society guideline 2007, whereas we assessed 289 patients in the other analysis. Rosuvastatin significantly slowed the percentage change in mean-IMT at 12 months compared with pravastatin (1.40 ± 10.03% versus 6.43 ± 13.77%, $P = 0.005$). LDL-C was reduced by 48.1% in the rosuvastatin group and 27.9% in the pravastatin group. The rate of achieving the LDL-C goal was significantly greater in the rosuvastatin group compared with the pravastatin group ($P < 0.001$). Rosuvastatin slowed the change in mean-IMT in the presence of every risk factor. Thus, intensive lipid-lowering therapy reduced progression of carotid IMT in high-risk patients. (Int Heart J 2014; 55: 146-152)

Key words: Atherosclerosis, Intensive statin therapy

Cardiovascular disease and cerebrovascular disease are clinical manifestations of atherosclerotic disease and major causes of death. Though the benefit of strict lipid control is established in Western high-risk patients, little research has been conducted in the Japanese population.

Carotid intima-media thickness (IMT) is a measure of atherosclerosis and increased IMT has been linked to prediction of future risk for myocardial infarction and stroke.[1-4] Carotid IMT is assessed noninvasively by ultrasonography and its change over time has been validated as a marker for the progression of atherosclerosis.[5,6]

We have conducted a study to compare the effect of intensive and conventional therapies in Japanese patients with atherosclerosis with low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL and max-IMT ≥ 1.1 mm; we reported that intensive therapy significantly slowed IMT progression.[7] Whereas it is still unclear what kind of patients with hypercholesterolemia might benefit from the intensive therapy.

We therefore planned a post-hoc analysis using the data from the Justification for Atherosclerosis Regression Treatment (JART) Study to compare the effect of intensive therapy with that of conventional therapy on IMT thickness in patients with risk factors for atherosclerosis.

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METHODS

Study design and ethical considerations: The rationale, design and main results of the JART Study have been previously reported.[7,8] The trial was conducted in accordance with the Declaration of Helsinki and the ethical principles for clinical studies in Japan. Its protocol was reviewed and approved by the institutional review board of each participating center. All patients provided written informed consent. The JART Study was a multicenter, randomized, open-label, blinded-endpoint (PROBE) study with 348 patients with hypercholesterolemia. This study was conducted at 15 hospitals and 5 clinics in Japan. Patients with elevated LDL-C (≥ 140 mg/dL) and a maximum IMT ≥ 1.1 mm were randomly assigned to either a rosuvastatin group (intensive therapy) or a pravastatin group (conventional therapy) using a dynamic allocation method with balancing factors of maximum IMT, serum LDL-C level, presence/absence of diabetes, and trial site.

The primary objective of the JART Study was to compare the effect of intensive therapy and conventional therapy on percentage change in mean-IMT. Patients were scheduled to undergo ultrasonographic examinations at baseline and 12 and 24 months. Serum lipid levels [ie, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)] were measured at baseline and follow-up visits including visits at 12 and 24 months. Serum LDL-C levels were measured using direct homogeneous assay, ie serum LDL-C levels were calculated using Friedewald's formula.[9] The JART Study was terminated early on the recommendation of the safety monitoring committee due to the superior effect seen in the rosuvastatin group. Therefore, the data at 12 months constituted the final results. The data at 24 months from the patients who completed visit 24 months before the study termination were also assessed as a reference.

For the post-hoc analysis, we planned two separate analyses using different patient populations. Prior to the main analysis, efficacy in patients with presence/absence of each independent risk factor was analyzed (Analysis 1). This analysis was planned because strict lipid control in patients with risks has recently gained attention in Japan. Subsequently, efficacy in patients assigned to the high-risk group was analyzed (Analysis 2). For Analysis 2 the population focused on the high-risk patient population in the JART Study. Safety in the high-risk patient group was also evaluated.

High-risk for the post-hoc analysis was defined as those patients classified as category III (primary prevention group with three or more major coronary risk factors as well as diabetes, cerebral infarction or arteriosclerosis obliterans) or secondary prevention according to the Japan Atherosclerosis Society guideline (JASG) 2007.[10] We included patients classified as category III in the high-risk group because the number of patients classified as secondary prevention was limited. Patient numbers in each analysis were as follows: 289 patients for Analysis 1, consisting of those patients for whom analysis data at 12 months was available, within the larger group of 298 patients (152 patients in the rosuvastatin group and 146 patients in the pravastatin group) who had completed 12 months follow-up from among the total efficacy population (n = 314); 200 patients for Analysis 2; and 215 patients for the safety analysis.

Study treatment: The LDL-C goal for intensive therapy was defined as < 80 mg/dL for primary prevention and < 70 mg/dL for secondary prevention. Patients were randomly assigned to receive rosuvastatin 5 mg or pravastatin 10 mg in a 1:1 ratio (step 1). Both treatments were administered once daily. If a patient did not achieve the LDL-C goal, the daily dose of rosuvastatin was increased to 10 mg (step 2), and prespecified lipid-lowering agents were added thereafter (step 3). The goal for conventional therapy was defined as < 160 mg/dL for category I (low-risk group), < 140 mg/dL for category II (intermediate-risk group), < 120 mg/dL for category III (high-risk group), and < 100 mg/dL for secondary prevention. If a patient did not achieve the target LDL-C goal, the daily dose of pravastatin was increased to 20 mg (step 2), and prespecified lipid-lowering agents were added thereafter (step 3).

Study assessment: Patients underwent ultrasonographic examinations at 0, 12, and 24 months, and B-mode images were obtained according to the guidelines for ultrasonic assessment of carotid artery disease.[11] For the measurement of carotid IMT, two 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 measured at the far wall of the common carotid artery in which the eligibility criterion of maximum IMT ≥ 1.1 mm was confirmed. A single observer who was blinded to the treatment assignments measured the mean-IMT in the core laboratory using Intimascope® (Media Cross Co. Ltd., Tokyo).[12]

Statistical analysis: In the post-hoc analysis, two separate analyses were planned in different patient populations. The population selected for Analysis 1 corresponded to the efficacy population in the JART Study. The population selected for Analysis 2 corresponded to the group of patients in category III or secondary prevention according to the JASG2007 in the efficacy population of the JART Study. The primary end point of the post-hoc analysis was the change in mean-IMT at 12 months in the high-risk group of patients for Analysis 2. Change in mean-IMT and lipid parameters at 24 months was also assessed using available data.

Efficacy population included all randomized patients who met major eligibility criteria, received at least one dose of trial treatment and had at least one assessment for carotid IMT according to the International Conference on Harmonisation guidelines. Safety analysis included all patients who received at least one dose of trial treatment and had at least one safety assessment.

In Analysis 1, mean changes (mm) and 95% confidence intervals for each risk factor were evaluated. In Analysis 2, between-group comparisons at baseline were performed using the chi-square test. Percentage changes in mean-IMT were compared between the treatment groups using t-tests. Changes of continuous variables were compared using t-tests and the percentages of categorical variables were compared using Fisher's exact test.

All data were analyzed using SAS® System Release 9.2 (SAS Institute, Cary, NC). All reported P values are 2-sided.

RESULTS

Patient characteristics: The population for Analysis 1 was the efficacy population of the JART Study and the baseline characteristics were well balanced between the treatment groups.[7]

For Analysis 2, the baseline characteristics were well balanced between the treatment groups (Table I). Approximately 25% of patients were classed as secondary prevention due to cardiovascular events in their medical history and about 75% were classed as category III according to the JASG2007. Lipid parameters at baseline were similar between treatment groups (Table I). Mean LDL-C level was 163.7 mg/dL in the rosuvastatin group and 165.6 mg/dL in the pravastatin group. Mean daily doses at 12 months were 7.78 ± 2.9 mg (mean ± SD) in the rosuvastatin group and 15.4 ± 5.0 mg in the pravastatin group.

Changes in carotid IMT in the presence of risk factors [Analysis 1]: Differences in the change of mean-IMT are shown in Figure 1. For every risk factor we evaluated, the change in mean-IMT was slower in the rosuvastatin group compared to the pravastatin group. Among the risk factors, statistical differences in favor of the rosuvastatin group were observed for elderly ≥ 65 years (mean difference, –0.0505 [95% confidence interval (CI), –0.0841 to –0.0169 mm]; $P = 0.0035$), presence of hypertension (–0.0352 [95% CI, –0.064 to –0.00641 mm]; $P = 0.0168$), and female gender (–0.0407 [95% CI, –0.0704 to –0.011 mm]; $P = 0.0076$). Although a statistical difference was not observed for diabetes, rosuvastatin slowed the change compared to pravastatin in this case (–0.028 [95%CI, –0.0588 to 0.0028 mm]; $P = 0.074$).

Changes in carotid IMT [Analysis 2]: Percentage change in mean-IMT (% change) at 12 months was 1.40 ± 10.03% (mean ± SD) in the rosuvastatin group and 6.43 ± 13.77% in the pravastatin group, and there was a significant difference in favor of the rosuvastatin group ($P = 0.005$). Similarly, rosuvastatin significantly slowed the percentage change in mean-IMT at 24 months (0.09 ± 11.27%) compared with pravastatin (7.52 ± 16.09%; between-group comparison, $P = 0.012$).

Similar results were found in the measured changes in mean-IMT (mm) at 12 months (Figure 2). The measured changes in mean-IMT in the rosuvastatin group were 0.0088 ± 0.0940 mm at 12 months and –0.0073 ± 0.1075 mm at 24 months ($P = 0.361$ and $P = 0.650$, respectively; compared with baseline). Corresponding changes in the pravastatin group were 0.0453 ± 0.1085 mm at 12 months and 0.0511 ± 0.1485 mm at 24 months ($P = 0.0002$ and $P = 0.023$, respectively; compared with baseline). Rosuvastatin significantly slowed progression of mean-IMT compared with pravastatin ($P = 0.015$). Moreover, at 24 months, rosuvastatin induced mean-IMT regression, whereas mean-IMT was stable in the pravastatin group ($P = 0.034$).

Changes in serum lipid levels in the patients for Analysis 2: Rosuvastatin resulted in significantly greater reductions over pravastatin in mean serum levels of LDL-C, TG, LDL-C/HDL-C ratio, and nonHDL-C (Table II). At 12 months, LDL-C in the rosuvastatin group was 83.3 ± 25.7 mg/dL (48.1% decrease), whereas that in the pravastatin group was 116.8 ± 22.3 mg/dL (27.9% decrease). Almost the same reductions in LDL-C were seen in both groups at 24 months.

While both treatments improved lipid management, 92 patients (87.6%) in the rosuvastatin group and 46 patients

Table I. Baseline Characteristics in High-Risk* Group**

	Rosuvastatin $n = 105$	Pravastatin $n = 95$
Sex, Male (%)	57 (54.3)	55 (57.9)
Age (mean ± SD) (years)	65.0 ± 8.3	63.8 ± 9.3
Elderly, ≥ 65 years (%)	58 (55.2)	49 (51.6)
Blood pressure (mean ± SD) (mmHg) (*n*)		
Systolic	133.1 ± 16.8 (105)	131.4 ± 18.9 (95)
Diastolic	76.3 ± 11.4 (105)	73.1 ± 13.8 (95)
JASG2007 category (%)		
III	79 (75.2)	72 (75.8)
Secondary prevention	26 (24.8)	23 (24.2)
CAD risk factors (%)		
Smoking	24 (22.9)	29 (30.5)
Family history of premature CAD	24 (22.9)	19 (20.0)
Medical history (%)		
Hypertension	76 (72.4)	69 (72.6)
Diabetes mellitus	70 (66.7)	68 (71.6)
Low HDL-C	11 (10.5)	15 (15.8)
Cerebral infarction	6 (5.7)	7 (7.4)
Peripheral arterial disease	4 (3.8)	2 (2.1)
CAD	26 (24.8)	23 (24.2)
Other medical treatment (%)		
Antihypertensive drug	67 (63.8)	58 (61.1)
Antidiabetic drug	37 (35.2)	39 (41.1)
LDL-C (mean ± SD) (mg/dL) *** (*n*)	163.7 ± 28.2 (103)	165.6 ± 29.9 (93)
HbA1c [NGSP] (mean ± SD) (%) (*n*)	6.47 ± 0.92 (99)	6.58 ± 0.92 (94)
Carotid IMT (mm) (*n*)		
Mean-IMT+	0.962 ± 0.234 (103)	0.862 ± 0.206 (95)

JASG indicates Japan Atherosclerosis Society guideline; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program; IMT, intima-media thickness; *, high-risk: category III or secondary prevention according to the JASG2007; **, Baseline parameters measured in high-risk patients; ***, Friedewald formula: LDL-C = total cholesterol - HDL-C - (triglyceride/5); +, There was a statistically significant difference between the groups ($P < 0.01$).

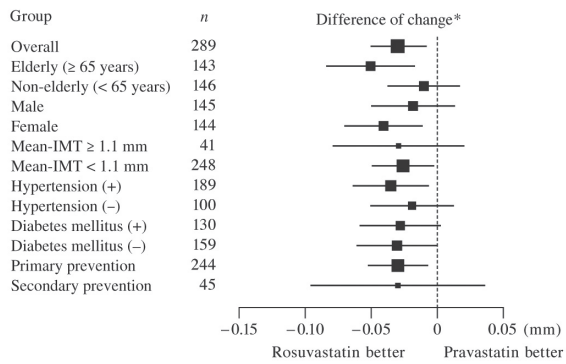

Figure 1. Difference in the Changes in Mean-IMT at 12 Months. * indicates difference in change shows mean values and 95% confidence interval (CI).

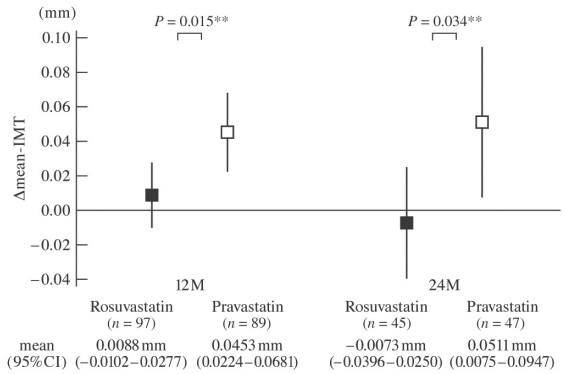

Figure 2. Changes in Mean-IMT in High-Risk Group*. * indicates category III or secondary prevention according to the Japan Atherosclerosis Society guideline 2007; **, unpaired *t*-test.

Table II. Changes in Lipid Profile in High-Risk* Group**

		Rosuvastatin	Change (%)	Pravastatin	Change (%)	Difference	P***
LDL-C+ (mg/dL)	Baseline	163.7 ± 28.2 (103)		165.6 ± 29.9 (93)			
	12 months	83.3 ± 25.7 (96)	–48.1 ± 18.6 (96)	116.8 ± 22.3 (89)	–27.9 ± 13.2 (87)	–20.2 ± 16.3	< 0.0001
	24 months	86.7 ± 22.8 (49)	–47.3 ± 16.8 (49)	120.4 ± 21.9 (42)	–27.3 ± 13.1 (42)	–20.0 ± 15.2	< 0.0001
HDL-C (mg/dL)	Baseline	52.9 ± 11.7 (103)		52.3 ± 12.9 (94)			
	12 months	57.8 ± 13.8 (97)	10.1 ± 18.6 (97)	56.8 ± 16.4 (90)	9.2 ± 21.4 (89)	0.9 ± 20.0	0.771
	24 months	56.9 ± 15.8 (49)	8.9 ± 22.2 (49)	57.4 ± 14.8 (43)	7.8 ± 19.0 (43)	1.0 ± 20.7	0.815
TG (mg/dL)	Baseline	154.4 ± 70.4 (103)		139.1 ± 72.4 (94)			
	12 months	122.9 ± 62.9 (97)	–12.8 ± 39.9 (97)	133.6 ± 70.8 (90)	4.9 ± 43.2 (89)	–17.7 ± 41.5	0.004
	24 months	120.3 ± 52.8 (49)	–18.3 ± 35.4 (49)	126.2 ± 70.5 (43)	11.2 ± 64.1 (43)	–29.5 ± 50.8	0.007
LDL-C/HDL-C ratio	Baseline	3.2 ± 0.9 (103)		3.4 ± 1.2 (93)			
	12 months	1.5 ± 0.7 (96)	–51.6 ± 19.4 (96)	2.2 ± 0.7 (89)	–31.9 ± 17.9 (87)	–19.7 ± 18.7	< 0.0001
	24 months	1.6 ± 0.6 (49)	–50.3 ± 15.5 (49)	2.2 ± 0.7 (42)	–31.1 ± 14.7 (42)	–19.2 ± 15.1	< 0.0001
non HDL-C (mg/dL)	Baseline	194.6 ± 29.3 (103)		192.7 ± 33.0 (94)			
	12 months	107.1 ± 28.0 (97)	–44.4 ± 14.9 (97)	143.5 ± 26.2 (90)	–23.9 ± 13.3 (89)	–20.5 ± 14.2	< 0.0001
	24 months	110.7 ± 24.0 (49)	–43.7 ± 15.2 (49)	144.4 ± 22.6 (43)	–24.2 ± 12.8 (43)	–19.5 ± 14.1	< 0.0001

Data are mean ± SD, ( ) = *n*. LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; *, category III or secondary prevention according to the Japan Atherosclerosis Society guideline (JASG) 2007; **, Baseline parameters measured in high-risk patients; ***, unpaired *t*-test; +, Friedewald formula: LDL-C = TC - HDL-C - (TG/5); ++, Data of patients who had completed 24 months follow-up at study discontinuation.

(48.4%) in the pravastatin group achieved the LDL-C goal at 12 months and there was a significant difference in favor of the rosuvastatin group ($P < 0.001$).

Safety in the patients for Analysis 2: The incidence of adverse events was a result of an imbalance between the rosuvastatin (65 events [57.5%]) and pravastatin groups (38 events [37.3%]). Frequently reported adverse events (incidence ≥ 3) in the rosuvastatin group were myalgia (4.42%), elevated creatine phosphokinase (3.54%), arthralgia (3.54%), rash (2.65%), and itching (2.65%). In the pravastatin group, coronary angioplasty (2.94%) was frequently seen.

On one hand, the incidence of serious adverse events was similar between treatment groups (16 events [14.2%] in the rosuvastatin group versus 14 events [13.7%] in the pravastatin group). Frequently reported serious adverse events (incidence ≥ 2) in the rosuvastatin group were pneumonia (1.77%), but included acute myocardial infarction and coronary angioplasty (1.96%) in the pravastatin group. Clinically important serious adverse events reported in the rosuvastatin group were coronary stenosis and lacunar infarction, while one death and one case of rhabdomyolysis were reported in the pravastatin group. Other adverse events were mild and/or transient in both groups.

Discussion

Post-hoc analysis of the JART Study shows that intensive therapy with rosuvastatin significantly slowed progression of mean-IMT and lowered LDL-C over conventional therapy with pravastatin in the high-risk patient group. Our result also shows that intensive therapy induced slower IMT progression in the presence of each risk factor. Intensive statin therapy may be useful for slowing IMT progression in the high-risk group of Japanese patients with atherosclerosis.

Carotid IMT is influenced by multiple cardiovascular risk factors, not only hypercholesterolemia, but other factors such as hypertension, diabetes mellitus, and aging.[13,14] Increased IMT has been linked to increased cardiovascular and cerebrovascular risk.[15-17]

Prior to Analysis 2 for the high-risk group, we assessed the effect on IMT progression of each independent risk factor in the efficacy population of the JART Study. Although there was no statistically significant difference between the rosuvastatin and pravastatin groups in the change in mean-IMT in diabetes patients, we thought the results in the rosuvastatin group were slightly better than those in the pravastatin group for slowing the progression of IMT (%change in mean-IMT: 1.21 ± 9.67% in the rosuvastatin group, 4.93 ± 11.03% in the pravastatin group, $P = 0.043$). Intensive therapy tended to slow IMT progression compared with conventional therapy, independent of the presence of each risk factor.

Taken together, these findings indicate that intensive rosuvastatin therapy is effective in patients with individual risk factors, even with more heavily weighted risk factors, as well as in patients without the corresponding risk factors. Thus, the equivalent treatment effect in patients classified as primary prevention is considered promising.

Rosuvastatin significantly slowed progression of mean-IMT compared with pravastatin at 12 months in the high-risk group of patients specified by the JASG2007. Moreover, rosuvastatin caused no change in mean-IMT at 12 months, and induced regression at 24 months although there is no statistically different change from baseline.

This finding is congruent with those reported in other studies on the effect of statin therapy on progression of IMT.[18,19] In the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) study, the rosuvastatin group (40 mg/day) induced IMT regression whereas progression was observed in the placebo group.[18] In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) study, mean-IMT was decreased in the atorvastatin group (80 mg/day) over 12 months while IMT was stable with the active comparator, pravastatin (40 mg/day).[19]

The patients in both the METEOR and ARBITER studies included lower risk groups (eg, patients with "zero to one risk factor" according to National Cholesterol Education Program (NCEP) Adult Treatment Panel (APT) III criteria[20] who were comparable to the intermediate-risk group by the JASG2007.[10]) On the one hand, our finding supports the idea that intensive statin therapy could benefit patients belonging to high-risk groups.

Furthermore, progressive IMT regression was found at 24 months, although the number of patients was limited, suggesting that longer-lasting intensive therapy induces continuous IMT regression.

We could not evaluate the association between slowed IMT progression and reduction in cardiovascular events in this study, due to the limited number of patients as a result of early termination of the JART Study. IMT is a surrogate cardiovascular endpoint[21,22] and its association with clinical events has been widely reported in the literature.

In a meta-analysis of 10 statin studies in patients without established cardiovascular disease, but with cardiovascular risk factors, statins significantly reduced the risk of major coronary events by 30% and major cerebrovascular events by 20%. Treatment effect was unchanged between clinical subgroups (eg, aging, diabetes mellitus).[23]

Based on these factors, although it should be verified and established in further large-scale studies, our study supports the view that intensive statin therapy can reduce cardiovascular events in high-risk groups of patients by slowing IMT progression.

Our study showed that intensive rosuvastatin therapy (average dosage at 12 months: 7.78 mg) induced a greater reduction of LDL-C (48.1% decrease). The reduction ratio is equivalent to the result of the JART Study (47.9% decrease) which includes low to moderate risk patients.[7]

Moreover, intensive therapy led to a higher achievement ratio of the LDL-C goal (87.6%) compared to conventional pravastatin therapy at 12 months. Although these are reference data, a similar reduction rate and achievement ratio of LDL-C goal was shown at 24 months; this means that rosuvastatin has the potency to induce progressive lipid lowering effects over a longer duration.

In Japan, the achievement ratio of the LDL-C goal for high-risk groups of patients is not yet satisfactory. Potent statins are currently available, but nevertheless, control of lipid parameters can stand further improvement. According to recent epidemiologic data, 36.5% and 10.4% of Japanese patients with atherosclerosis were classified as category III and secondary prevention, respectively, according to the JASG 2007,[10] ie about half of the Japanese patients were categorized as high-risk. Nevertheless, achievement rates of the LDL-C goal for patients classed as category III or secondary prevention were 30 - 50% in Japan. The achievement rate with atorvastatin treatment, which was the only available potent statin at the time of the survey, was about 70%.[24]

Likewise, in Western countries, a large number of patients in high-risk groups did not attain the LDL-C goal recommended in the NCEP APT III guidelines. Achievement rates of the LDL-C goal were 55% in patients with diabetes mellitus, and 62% in patients with coronary heart disease.[25]

Both rosuvastatin and pravastatin were reasonably well tolerated in the high-risk patient group. Larger numbers of patients complained of adverse events in the rosuvastatin group compared with the pravastatin group, but incidence rates in both groups were similar to the main findings of the JART Study which included low-risk and intermediate-risk groups of patients.[7] Incidence rate of serious adverse events was similar between treatment groups and a small number of clinically important events were observed in both groups. These results suggest that high-risk groups of patients can safely receive intensive lipid-lowering therapy.

Limitations in the study should be addressed. The number of patients in the sub-group analysis was limited because this ad-hoc analysis focusing on a high-risk group of patients was planned after termination of the study. In addition, the JART Study itself was terminated early in accordance with the recommendation of the safety monitoring committee, due to the superior effect of rosuvastatin on carotid IMT progression detected in the scheduled interim analysis. Longer duration randomized trials are needed to reproduce our findings or to build evidence for a relationship between carotid IMT progression and the clinical events of atherosclerosis.

Conclusion: The findings in this study demonstrate that in a high-risk group of patients with atherosclerosis, intensive therapy resulted in statistically significant reductions in the rate of progression of mean-IMT at 12 months compared with conventional therapy. Also, the efficacy of intensive statin therapy with respect to every major risk factor shown in Analysis 1 is

regarded as supporting the results in Analyisis 2 for the high-risk group.

This provides the important information that intensive statin therapy may be useful in slowing the progression of atherosclerosis in high-risk groups of patients.

We expect that further studies will clarify the associations between slowing IMT progression, LDL-C reduction, and clinical events. Such studies, however, should be planned and conducted in as ethical and careful a manner as possible, because a large difference regarding the effect on IMT progression was observed between intensive therapy and conventional therapy within a short time interval.

Disclosure

Conflicts of interest: Hiroyuki Daida, MD, received a grant, honorarium and payment for lectures from AstraZeneca K.K., Shionogi&Co, Ltd and Daiichi Sankyo Co, Ltd. Kohei Kaku, MD, received grants from AstraZeneca K.K. and Daiichi Sankyo Co, Ltd. Ryuzo Kawamori, MD, received consulting fees, honorarium and payment for lectures from AstraZeneca K.K. and Shionogi&Co, Ltd. Izuru Masuda, MD, received payment for lectures from AstraZeneca K.K. and Shionogi&Co, Ltd. Ichiro Sakuma, MD, received consulting fees from AstraZeneca K.K. Tsutomu Yamazaki, MD, received a grant and payment for lectures from AstraZeneca K.K. Masayuki Yoshida, MD, received honorarium and payment for lectures from AstraZeneca K.K. and Shionogi&Co, Ltd.

Appendix

The following persons participated in this trial.

Steering Committee: Ryuji Nohara (principal investigator and trial chair), Hiroyuki Daida, Mitsumasa Hata, Kohei Kaku, Ryuzo Kawamori, Masahiko Kurabayashi, Izuru Masuda, Ichiro Sakuma, Tsutomu Yamazaki, Hiroyoshi Yokoi, Masayuki Yoshida.

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