



High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD) A Randomized Superiority Trial

Editorials, see p 2010 and p 2013

BACKGROUND: Current guidelines call for high-intensity statin therapy in patients with cardiovascular disease on the basis of several previous “more versus less statins” trials. However, no clear evidence for more versus less statins has been established in an Asian population.

METHODS: In this prospective, multicenter, randomized, open-label, blinded end point study, 13 054 Japanese patients with stable coronary artery disease who achieved low-density lipoprotein cholesterol (LDL-C) <120 mg/dL during a run-in period (pitavastatin 1 mg/d) were randomized in a 1-to-1 fashion to high-dose (pitavastatin 4 mg/d; n=6526) or low-dose (pitavastatin 1 mg/d; n=6528) statin therapy. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization. The secondary composite end point was a composite of the primary end point and clinically indicated coronary revascularization excluding target-lesion revascularization at sites of prior percutaneous coronary intervention.

RESULTS: The mean age of the study population was 68 years, and 83% were male. The mean LDL-C level before enrollment was 93 mg/dL with 91% of patients taking statins. The baseline LDL-C level after the run-in period on pitavastatin 1 mg/d was 87.7 and 88.1 mg/dL in the high-dose and low-dose groups, respectively. During the entire course of follow-up, LDL-C in the high-dose group was lower by 14.7 mg/dL than in the low-dose group ($P<0.001$). With a median follow-up of 3.9 years, high-dose as compared with low-dose pitavastatin significantly reduced the risk of the primary end point (266 patients [4.3%] and 334 patients [5.4%]; hazard ratio, 0.81; 95% confidence interval, 0.69–0.95; $P=0.01$) and the risk of the secondary composite end point (489 patients [7.9%] and 600 patients [9.7%]; hazard ratio, 0.83; 95% confidence interval, 0.73–0.93; $P=0.002$). High-dose pitavastatin also significantly reduced the risks of several other secondary end points such as all-cause death, myocardial infarction, and clinically indicated coronary revascularization. The results for the primary and the secondary composite end points were consistent across several prespecified subgroups, including the low (<95 mg/dL) baseline LDL-C subgroup. Serious adverse event rates were low in both groups.

CONCLUSIONS: High-dose (4 mg/d) compared with low-dose (1 mg/d) pitavastatin therapy significantly reduced cardiovascular events in Japanese patients with stable coronary artery disease.

CLINICAL TRIAL REGISTRATION: URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT01042730.

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■ coronary artery disease
■ hydroxymethylglutaryl-CoA reductase inhibitors ■ long-term adverse effects
■ secondary prevention ■ stroke

Sources of Funding, see page 2006

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Clinical Perspective

What Is New?

- REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease) is currently the largest randomized trial to compare high-dose and low-dose statin therapy.
- It was also the first such trial performed in Asia.
- High-dose compared with low-dose pitavastatin significantly reduced the primary end point (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization).
- All-cause death, myocardial infarction, and clinically indicated coronary revascularization were also significantly reduced.
- Rates of serious adverse events were similar in the 2 treatment groups.

What Are the Clinical Implications?

- The results of the REAL-CAD study confirmed that high-dose compared with low-dose pitavastatin can safely improve the prevention of cardiovascular events in Japanese patients with coronary artery disease, who commonly receive low-intensity statin therapy.
- REAL-CAD is a practice-changing trial, suggesting that the administration of maximum tolerable doses of statins, within the range of local approval, would be the preferred statin strategy in patients with established coronary artery disease regardless of baseline low-density lipoprotein cholesterol levels.

Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for cardiovascular events,¹ and lowering LDL-C with statins has proved effective for primary and secondary prevention of coronary artery disease (CAD).^{2–9} Several previous “more versus less statins” trials in patients with CAD demonstrated that high-intensity statin therapy significantly reduced cardiovascular events compared with moderate-intensity statin therapy.^{10–14} On the basis of these results, the current American College of Cardiology/American Heart Association guideline recommends high-intensity statin therapy in patients ≤ 75 years of age with clinical atherosclerotic cardiovascular disease,¹⁵ whereas the current European Society of Cardiology guideline recommends an LDL-C target of ≤ 70 mg/dL for patients with very high cardiovascular risk.¹⁶ However, high-intensity statin therapy is not widely implemented in daily clinical practice, particularly in Asia, at least partly because there has been no previous trials of more versus less statins in Asia.^{17–19} Therefore, we conducted a

large outcome trial comparing the efficacy of high-dose versus low-dose statin therapy in patients with established stable CAD in Japan. Our goal was to determine whether higher-dose statin therapy would be beneficial and safe in Japanese patients.

METHODS

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design

The REAL-CAD study (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease) is a prospective, multicenter, randomized, open-label, blinded end point, physician-initiated superiority trial to determine whether high-dose (4 mg/d) compared with low-dose (1 mg/d) pitavastatin therapy could reduce cardiovascular events in Japanese patients with stable CAD. Pitavastatin is a statin with potent LDL-C-lowering effects developed by Kowa Pharmaceutical Co Ltd (Tokyo, Japan). Pitavastatin doses of 1 and 4 mg were reported to reduce LDL-C by 33.6% and 47.2%, respectively, in Japanese patients.²⁰ A similar magnitude of LDL-C reduction was also reported in white and East Asian patients.^{21–23} Pitavastatin 4 mg is the maximum approved dose in Japan and has demonstrated effects comparable to atorvastatin 20 mg in terms of both LDL-C reduction and coronary plaque regression assessed by intravascular ultrasound, whereas pitavastatin 1 mg has an LDL-C-lowering effect comparable to that of atorvastatin 5 mg.^{24,25}

Eligible patients were men and women 20 to 80 years of age with stable CAD as defined by a history of acute coronary syndrome or coronary revascularization >3 months ago or a clinical diagnosis of CAD with angiographically documented coronary artery stenosis of at least 75% diameter narrowing according to the American Heart Association classification.²⁶ We excluded those patients with LDL-C <100 mg/dL without statin therapy before enrollment because the label in the instructions for pitavastatin restricted use to patients with hypercholesterolemia. Detailed inclusion and exclusion criteria are provided in the [online-only Data Supplement](#). Patients were enrolled on an outpatient basis through academic and general hospitals and clinics across Japan. Eligible patients who provided informed consent were enrolled and received pitavastatin 1 mg once daily orally for a run-in period of at least 1 month. Patients were evaluated for secondary eligibility, excluding those patients with LDL-C ≥ 120 mg/dL after the run-in period, onset of acute coronary syndrome and/or coronary revascularization within the past 3 months, poor medication adherence to pitavastatin, occurrence of primary end point events, or adverse events prohibiting study continuation during the run-in period.

Patients who met the secondary eligibility criteria were randomized in a 1-to-1 fashion to oral pitavastatin, either 4 mg/d (high-dose group) or 1 mg/d (low-dose group), with an electronic data capture system and dynamic allocation stratified by facility, age (<65 or ≥ 65 years), sex, diabetes mellitus, and statin use before enrollment. The assignment algorithm

was determined by the study statistician. This is an open-label trial. However, the independent event committee adjudicated all the end point events while blinded to the assigned group ([online-only Data Supplement](#)).

During follow-up, the patients' visits dictated by the protocol were at 6 and 12 months in the first year and every 12 months thereafter. Serum lipid levels such as LDL-C, total cholesterol, triglycerides, and high-density lipoprotein cholesterol, as well as other blood tests such as creatine kinase, alanine aminotransferase, aspartate aminotransferase, creatinine, and hemoglobin A_{1c}, were to be measured at baseline, at 6 and 12 months, and yearly thereafter, whereas high-sensitivity C-reactive protein (hsCRP) was to be measured at baseline and at 6 months.

The site investigators reported follow-up information through the web-based electronic data capturing system. Data were monitored by the data center, and the logical inconsistencies were resolved by queries. Final clinical follow-up data were collected through January to March 2016. From 2012 to 2016, site audits were performed for 3914 patients from 28 centers, and the independent data monitoring committee regularly assessed the safety aspect of study conduct.

End Points

The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization. Cardiovascular death consisted of cardiac death, including sudden death and cardiac procedure-related death, as well as noncardiac vascular death. Death without obvious noncardiovascular cause was regarded as cardiovascular death. Myocardial infarction was defined as described by the Academic Research Consortium (ARC).²⁷ A secondary composite end point including coronary revascularization was defined as a composite of the primary end point event and clinically indicated coronary revascularization, excluding target-lesion revascularization for lesions treated at prior percutaneous coronary intervention. Target-lesion revascularization was not included in this secondary end point because it was unknown whether statins are effective in preventing restenosis and/or thrombosis of lesions treated at prior percutaneous coronary intervention. Other secondary end points and the details for the definitions of end points are described in the [online-only Data Supplement](#).

The study also evaluated adverse events that developed after the start of the assigned treatment and for which a causal relationship to study drug administration could not be ruled out. Adverse events were assessed and reported by the site investigators.

Statistical Analysis

From the previous trials of more versus less statins, we hypothesized that the present study would show 16% relative risk reduction with the high-dose pitavastatin treatment.²⁸ A total of 1033 events would be required to detect a 16% relative risk reduction with 80% statistical power and a 2-sided α of 5%.²⁹ Assuming an annual event rate of 2.5% based on the previous Japanese studies^{30–32} and an estimated dropout rate of 10%, a total of 12 600 patients would be required to

achieve 1033 events during the planned 3 years of enrollment and at least 3 years of follow-up.

The actual event rate was lower than anticipated. However, on October 27, 2015, the steering committee decided not to extend the study further despite the original event-driven trial design because a substantial number of centers were reluctant to extend the study further.

The cumulative incidence of clinical events was estimated by the Kaplan-Meier method and compared by the log-rank test. The effect of the high-dose pitavastatin relative to the low-dose pitavastatin was assessed by the Cox proportional hazard model and was expressed as hazard ratio with 95% confidence interval. Proportional hazard assumptions were assessed on the plots of log (time) versus log [–log (survival)], and the assumptions were verified. Adherence to the study drug was assessed by the time-to-event analysis in which nonadherence was regarded as the event. Nonadherence to the study drug included <50% intake of the study drug, discontinuation of the assigned treatment, and loss of the drug adherence data.

Safety analyses were conducted using the data from all enrolled patients who had received at least 1 dose of pitavastatin and for whom postdose data were available (safety analysis set). Efficacy analyses were conducted after the exclusion of those patients who were randomized but were found not to meet the eligibility criteria (full analysis set). We conducted a sensitivity analysis in the safety analysis set population without exclusion of those randomized patients who did not meet inclusion and exclusion criteria. Patients lost to follow-up were censored at the time when their final clinical follow-up information was available. Number needed to treat during the 5-year follow-up was estimated from the event rate at 4 years because the number of patients at risk decreased substantially at 5 years.

We performed subgroup analyses for the primary and secondary composite end points in several prespecified subgroups. The formal interaction test was performed between the subgroup factors and the effect of the high-dose pitavastatin relative to the low-dose pitavastatin. Time-varying measurements such as LDL-C were analyzed with the generalized estimating equation models with robust variance adjustment and compound symmetry structure used as the initial assumption. Triglycerides and hsCRP were analyzed after log transformation. For describing the time profile, the average value (least-squares means) including the baseline was estimated for each of the groups with time-group interaction terms as covariates in the generalized estimating equation model for accommodating missing values. Time variables were modeled as categorical (dummy) variables. Group difference (treatment effect) and time-group interaction after the intervention were estimated with time, group, time-interaction and the baseline value as covariates. The baseline value was included in the model for reducing bias and variability resulting from the regression to the mean. Missing values were not imputed in the analyses.

Dr Ohashi was responsible for the analysis results as the statistician for this trial. All statistical analyses were conducted with SAS System Release 9.4 software. All *P* values are 2 sided.

The Steering Committee ([online-only Data Supplement](#)) designed the trial. All authors agreed to submit the manuscript for publication and vouch for adherence to the study

protocol and for the accuracy and completeness of the data. The Comprehensive Support Project for Clinical Research of Lifestyle-Related Disease of the Public Health Research Foundation funded this study. The company manufacturing the study drug (Kowa Pharmaceutical Co Ltd) provided financial support but was not involved in design, analysis, data interpretation, or manuscript preparation. Ethics approval was granted by the Public Health Research Foundation ethics review committee and by ethics committees at all participating sites. All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Study Patients

From January 31, 2010, to March 31, 2013, a total of 14 774 patients were enrolled from 733 academic and general hospitals and clinics across Japan. After completion of the run-in period, 13 054 patients were randomized to either high-dose ($n=6526$) or low-dose ($n=6528$) pitavastatin. The safety analysis population consisted of 12 818 patients (high-dose, $n=6390$; low-dose, $n=6428$) after the exclusion of those patients who withdrew consent or for whom written informed consent was missing at the time of the site audits. The full analysis population consisted of 12 413 patients (high-dose, $n=6199$; low-dose, $n=6214$) after the exclusion of those patients who were found not to meet the eligibility criteria. The median follow-up period for the survivors was similar for the high-dose and low-dose groups (3.9 [range, 0.0–5.8] years and

3.9 [range, 0.0–5.9] years; $P=0.08$). Follow-up at 1 year was completed in 5607 patients (97.0%) in the high-dose group and in 5809 patients (96.9%) in the low-dose group. Final follow-up data beyond January 2016 were available for 5171 patients (83.4%) and for 5169 patients (83.2%), respectively (Figure 1). The rate of adherence to the study drug was high in both groups, although it was slightly but significantly lower in the high-dose group than in the low-dose group (97.1% and 98.7% at 6 months, 74.8% and 76.8% at 4 years; $P=0.02$; Figure 1 in the online-only Data Supplement).

The study population represented typical Japanese patients with stable CAD, with advanced age and a preponderance of male sex. Hypertension was present in 76% of patients and diabetes mellitus in 40%. A total of 51% had prior myocardial infarction, and 90% had prior coronary revascularization predominantly by percutaneous coronary intervention. For baseline medications, antiplatelet therapy, including dual therapy, was widely used, whereas the use of β -blockers was less prevalent. The baseline characteristics and medications were well balanced between the 2 groups (Table 1).

Lipid Parameters and hsCRP

The mean LDL-C before enrollment was 93 mg/dL with 91% of patients taking statins. The baseline LDL-C level after the run-in period was 87.7 and 88.1 mg/dL in the high-dose and low-dose groups, respectively. At 6 months, the LDL-C level was reduced by 16% (73.7

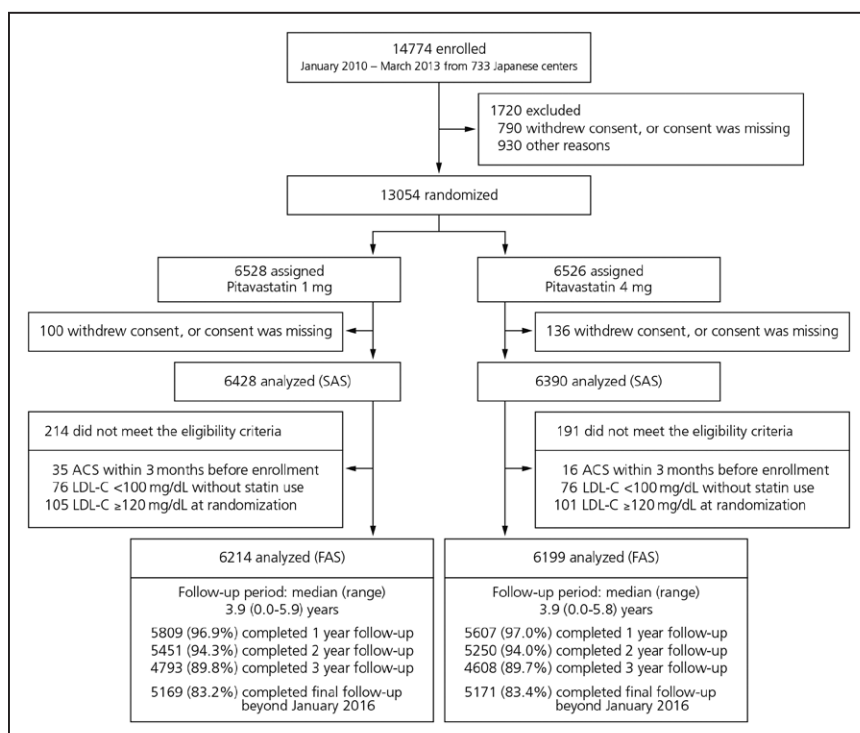


Figure 1. Disposition of patients.

The reasons for not meeting the eligibility criteria were not mutually exclusive. ACS indicates acute coronary syndrome; FAS, full analysis set; LDL-C, low-density lipoprotein cholesterol; and SAS, safety analysis set.

Table 1. Baseline Characteristics

Variable	Pitavastatin 1 mg (n=6214)	Pitavastatin 4 mg (n=6199)
Age, y	68.1 (8.3)	68.0 (8.3)
Male, n (%)	5124 (82.5)	5129 (82.7)
Weight, kg	65.1 (11.3) (n=5874)*	65.2 (11.2) (n=5822)*
Body mass index, kg/m ²	24.6 (3.4) (n=5771)*	24.6 (3.3) (n=5710)*
Abdominal circumference, cm	88.0 (9.6) (n=5069)*	88.1 (9.3) (n=5038)*
Systolic blood pressure, mmHg	127.4 (16.1) (n=6008)*	127.8 (16.2) (n=5967)*
Diastolic blood pressure, mmHg	72.9 (10.8) (n=6008)*	73.0 (10.8) (n=5967)*
Heart rate, bpm	69.6 (11.4) (n=5780)*	69.5 (11.7) (n=5730)*
Left ventricular ejection fraction, %	60.0 (11.5) (n=3203)*	60.3 (11.6) (n=3192)*
Cardiovascular history		
History of acute coronary syndrome, n (%)	4465 (71.9)	4450 (71.8)
Duration from acute coronary syndrome to randomization, y	5.1 (5.3) (n=4389)*	4.9 (5.1) (n=4377)*
Acute coronary syndrome within 1 y before randomization, n (%)	1503 (24.2)	1494 (24.1)
Hospitalization for unstable angina, n (%)	1566 (25.2)	1601 (25.8)
Myocardial infarction, n (%)	3225 (51.9)	3159 (51.0)
Coronary revascularization, n (%)	5625 (90.5)	5601 (90.4)
Duration from revascularization to randomization, y	3.9 (4.2) (n=5567)*	3.9 (4.2) (n=5542)*
Revascularization within 1 y before randomization, n (%)	1722 (27.7)	1717 (27.7)
Percutaneous coronary intervention, n (%)	5170 (83.2)	5190 (83.7)
Coronary artery bypass grafting, n (%)	796 (12.8)	778 (12.6)
Congestive heart failure, n (%)	338 (5.4)	312 (5.0)
Atrial fibrillation, n (%)	388 (6.2)	382 (6.2)
Ischemic stroke, n (%)	429 (6.9)	421 (6.8)
Hemorrhagic stroke, n (%)	76 (1.2)	64 (1.0)
Peripheral vascular disease, n (%)	458 (7.4)	409 (6.6)
Current smoking, n (%)	989 (15.9)	1042 (16.8)
Diabetes mellitus, n (%)	2488 (40.0)	2490 (40.2)
Hypertension, n (%)	4688 (75.4)	4708 (75.9)
Family history of coronary artery disease, n (%)	1050 (16.9)	997 (16.1)
History of malignancy, n (%)	345 (5.6)	315 (5.1)
Blood examinations		
Total cholesterol, mg/dL†	166.8 (24.5) (n=6176)*	166.8 (24.1) (n=6153)*
LDL-C, mg/dL‡	88.1 (18.9)	87.7 (19.0)
HDL-C, mg/dL‡	50.7 (12.7) (n=6212)*	50.7 (12.5) (n=6198)*

(Continued)

Table 1. Continued

Variable	Pitavastatin 1 mg (n=6214)	Pitavastatin 4 mg (n=6199)
Triglycerides, mg/dL (median)†	124 (89–173) (n=6208)*	124 (89–177) (n=6195)*
Apolipoprotein A1, mg/dL	135.7 (24.7) (n=947)*	135.7 (24.8) (n=968)*
Apolipoprotein B, mg/dL	80.2 (15.4) (n=948)*	80.0 (15.3) (n=967)*
High-sensitivity C-reactive protein (median), mg/L†	0.52 (0.25–1.22) (n=6032)*	0.51 (0.24–1.15) (n=5994)*
≥2.0 mg/L, n (%)	894 (14.8)	862 (14.4)
Glucose, mg/dL	123.6 (40.6) (n=5023)*	124.6 (40.0) (n=4997)*
Hemoglobin A _{1c} , %	5.86 (0.85) (n=5777)*	5.86 (0.86) (n=5712)*
In patients with diabetes mellitus, %	6.48 (0.93) (n=2410/2488)*	6.46 (0.92) (n=2389/2490)*
Creatine kinase, U/L	125.9 (90.3) (n=5894)*	126.3 (92.8) (n=5871)*
Serum creatinine (median), mg/dL	0.87 (0.74–1.0) (n=6085)*	0.87 (0.74–1.0) (n=6033)*
eGFR, mL·min ⁻¹ ·1.73 m ⁻² §	65.8 (19.0) (n=6085)*	66.0 (17.3) (n=6033)*
Chronic kidney disease, n (%)	(n=6085)*	(n=6033)*
Stage 1	434 (7.1)	468 (7.8)
Stage 2	3450 (56.7)	3426 (56.8)
Stage 3	2097 (34.5)	2042 (33.8)
Stage 4	94 (1.5)	92 (1.5)
Stage 5	10 (0.2)	5 (0.1)
Medications, n (%)	(n=5759)*	(n=5690)*
Statins before run-in period	5656 (91.0)	5622 (90.7)
Aspirin	5329 (92.5)	5255 (92.4)
Thienopyridine	2719 (47.2)	2685 (47.2)
Dual antiplatelet therapy	2570 (44.6)	2500 (43.9)
β-Blocker	2443 (42.4)	2364 (41.5)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	3891 (67.6)	3830 (67.3)

Data are n (%), median (interquartile range), or mean (SD). No significant differences were noted between the groups.

eGFR indicates estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

*For the variables with missing values, we indicated the number of patients evaluated.

†Values were derived from central laboratory measurements. If a value from central laboratory measurement was missing or not calculable, a value obtained from insurance-covered measurement was used instead. If any value other than those centrally measured was missing, that value was not imputed from other data but was handled as a missing value and excluded from analysis. Central laboratory measurements at baseline were available for LDL-C in 11 813 patients and for total cholesterol, triglycerides, HDL-C, and high-sensitivity C-reactive protein in 12 026 patients.

‡Values were calculated with the Friedewald equation:

LDL-C=total cholesterol–(HDL-C+triglycerides/5) when triglyceride values are <400 mg/dL.

§eGFR was calculated by the following formula for Japanese patients. eGFR (male)=194×serum creatinine^{-1.094}×age^{-0.287}, and eGFR (female)=(194×serum creatinine^{-1.094}×age^{-0.287})×0.739.

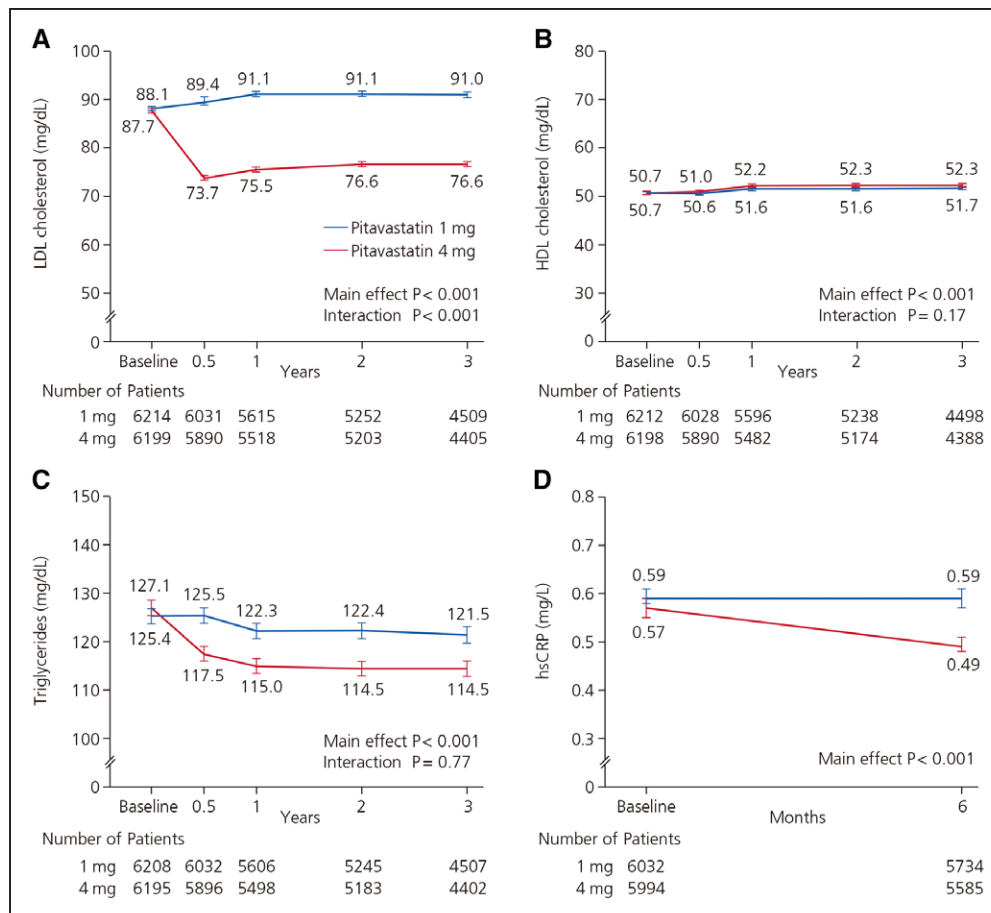


Figure 2. Changes in lipid parameters and high-sensitivity C-reactive protein (hsCRP) levels over time.

A through **C**, Changes over time in low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. **D**, Change in hsCRP from baseline to 6 months. Values at baseline and at 6 months were basically derived from central laboratory measurements. If a value from central laboratory measurement was not available or not calculable, a value obtained from the measurement at each institution was used instead. If any value other than those centrally measured was missing, that value was not imputed from other data but was handled as a missing value and excluded from analysis. Central laboratory measurements were available for LDL cholesterol in 11 813 patients at baseline and in 11 319 patients at 6 months, whereas those for total cholesterol, triglycerides, and HDL cholesterol were available in 12 026 patients at baseline and in 11 320 patients at 6 months. Central laboratory measurements for hsCRP were available in 12 026 patients at baseline and in 11 319 patients at 6 months. Values at 1, 2, and 3 years were derived from measurements at each institution. P values were for the main therapeutic effect and for the interaction effect between therapeutic effect and time.

mg/dL) in the high-dose group and was unchanged (89.4 mg/dL) in the low-dose group (Figure 2). During the entire course of follow-up, LDL-C in the high-dose group was lower by 14.7 mg/dL than in the low-dose group. Total cholesterol and triglyceride levels were also significantly lower and high-density lipoprotein cholesterol level was significantly higher in the high-dose group than in the low-dose group (Figure 2).

The level of hsCRP was similar and low in both the high-dose and low-dose groups (0.57 and 0.59 mg/L) at baseline but was significantly lower in the high-dose group than in the low-dose group at 6 months (0.49 and 0.59 mg/L; Figure 2). Blood pressure and hemoglobin A_{1c} were well controlled and similar in both groups during follow-up (Figure II in the online-only Data Supplement).

Clinical Outcomes

High-dose compared with low-dose pitavastatin significantly reduced the primary end point. The primary end point occurred in 266 patients (4.3%) in the high-dose group and 334 patients (5.4%) in the low-dose group (hazard ratio, 0.81; 95% confidence interval, 0.69–0.95; $P=0.01$; Table 2). The cumulative 4-year incidence of the primary end point was significantly lower in the high-dose group than in the low-dose group (4.6% and 5.6%; $P=0.01$; Figure 3 and Table 2). The number needed to treat for the prevention of 1 primary end point event was 63 during the 5 years of follow-up. In the sensitivity analysis without exclusion of those randomized patients who did not meet inclusion and exclusion criteria, the magnitude

Table 2. Primary and Secondary End Points

Outcomes	Patients With Event, n (%) Cumulative 4-y Incidence (95% Confidence Interval), %*		Hazard Ratio (95% Confidence Interval)†	P Value‡
	Pitavastatin 1 mg (n=6214)	Pitavastatin 4 mg (n=6199)		
Primary end point: a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization	334 (5.4) 5.6 (5.0–6.3)	266 (4.3) 4.6 (4.0–5.2)	0.81 (0.69–0.95)	0.01
Secondary end points				
Composite of primary end point or coronary revascularization	600 (9.7) 10.4 (9.6–11.2)	489 (7.9) 8.5 (7.7–9.3)	0.83 (0.73–0.93)	0.002
Death resulting from any cause	260 (4.2) 4.2 (3.7–4.8)	207 (3.3) 3.7 (3.2–4.3)	0.81 (0.68–0.98)	0.03
Cardiovascular death	112 (1.8) 1.8 (1.5–2.2)	86 (1.4) 1.5 (1.2–1.9)	0.78 (0.59–1.04)	0.09
Cardiac death	85 (1.4) 1.3 (1.0–1.7)	62 (1.0) 1.0 (0.8–1.4)	0.75 (0.54–1.03)	0.08
Myocardial infarction	72 (1.2) 1.3 (1.0–1.6)	40 (0.6) 0.8 (0.5–1.0)	0.57 (0.38–0.83)	0.004
Ischemic stroke	83 (1.3) 1.4 (1.1–1.8)	84 (1.4) 1.4 (1.1–1.8)	1.03 (0.76–1.40)	0.84
Hemorrhagic stroke	30 (0.5) 0.5 (0.3–0.7)	43 (0.7) 0.8 (0.6–1.1)	1.46 (0.92–2.33)	0.11
Unstable angina requiring emergency hospitalization	90 (1.4) 1.6 (1.3–2.0)	76 (1.2) 1.3 (1.0–1.6)	0.86 (0.63–1.17)	0.34
Coronary revascularization (all)	626 (10.1) 11.1 (10.2–12.0)	529 (8.5) 9.2 (8.5–10.1)	0.86 (0.76–0.96)	0.008
Coronary revascularization (nontarget-lesion revascularization)	356 (5.7) 6.4 (5.7–7.1)	277 (4.5) 4.9 (4.3–5.5)	0.79 (0.68–0.92)	0.003
Coronary revascularization (target-lesion revascularization)	319 (5.1) 5.6 (5.0–6.3)	276 (4.5) 4.8 (4.3–5.5)	0.88 (0.75–1.03)	0.12

Event rates were calculated as number of patients with the event divided by number of patients in the full analysis set population.

For the secondary composite end point, coronary revascularization excludes target-lesion revascularization for lesions treated at prior percutaneous coronary intervention.

*Cumulative 4-year incidence was estimated using the Kaplan-Meier method.

†Hazard ratios and P value were estimated using the univariate Cox proportional hazard model.

of risk reduction by high-dose pitavastatin for the primary end point (hazard ratio, 0.81; 95% confidence interval, 0.69–0.95, $P=0.01$) was consistent with that in the main analysis.

High-dose compared with low-dose pitavastatin also significantly reduced the secondary composite end point, including coronary revascularization, which occurred in 489 patients (7.9%) in the high-dose group and 600 patients (9.7%) in the low-dose group (hazard ratio, 0.83; 95% CI, 0.73–0.93; $P=0.002$; Table 2). The cumulative 4-year incidence of this secondary end point was also significantly lower in the high-dose group than in the low-dose group (8.5% and 10.4%; $P=0.002$) with a number needed to treat of 41 during the 5 years of follow-up (Figure 3 and Table 2).

High-dose pitavastatin also significantly reduced the risks of several other secondary end points such as all-cause death, myocardial infarction, and clinically indicated coronary revascularization. There was no significant difference in the risk of ischemic stroke, hemor-

rhagic stroke, or unstable angina requiring emergency hospitalization (Table 2).

The risk reduction for the primary end point and for the secondary composite end point, including coronary revascularization, by the high-dose pitavastatin was consistent across all the prespecified subgroups such as age (≥ 65 and <65 years), sex, diabetes mellitus, baseline LDL-C (≥ 95 and <95 mg/dL), high-density lipoprotein cholesterol (>40 and ≤ 40 mg/dL), triglycerides (≥ 150 and <150 mg/dL), and hsCRP levels (≥ 1 and <1 mg/L) and body mass index (≥ 25 and <25 kg/m²) without any significant interaction between the subgroup factors and the effect of high-dose pitavastatin (Figure 4). The magnitude of risk reduction by the high-dose pitavastatin in the low baseline LDL cholesterol subgroup was comparable to that in the high baseline LDL cholesterol subgroup.

The rates of serious adverse events, including rhabdomyolysis, were low and did not differ between the 2 groups, although muscle complaints were reported more often in the high-dose group than in the low-

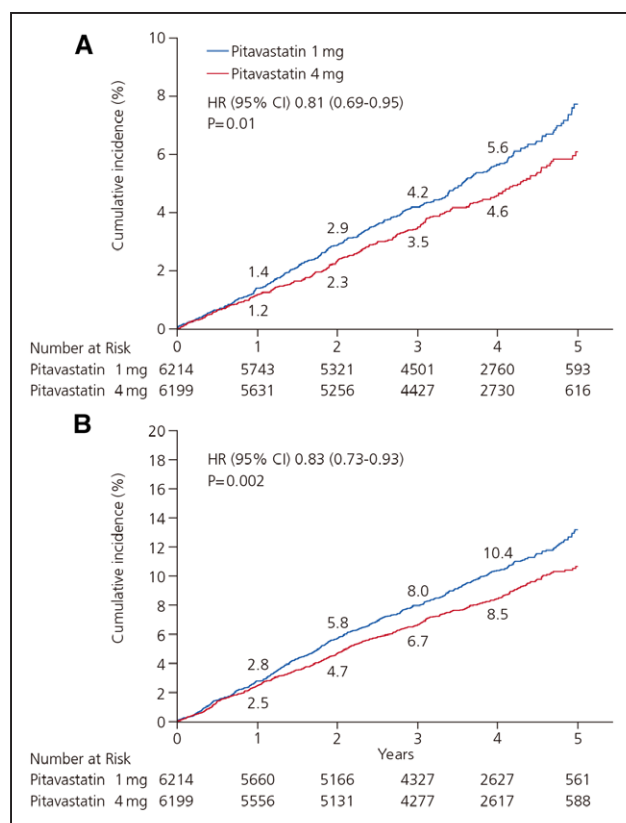


Figure 3. Kaplan-Meier curves for the primary end point and a secondary composite end point (primary end point plus coronary revascularization).

The cumulative incidence was estimated by the Kaplan-Meier method. **A** and **B**, Kaplan-Meier curves for the primary end point (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization) and for a secondary composite end point (a composite of primary end point or coronary revascularization based on clinical indication), respectively. Coronary revascularization as a component of the secondary composite end point excluded target-lesion revascularization for lesions treated at the time of prior percutaneous coronary intervention. CI indicates confidence interval; and HR, hazard ratio.

dose group. However, the rate of creatine kinase elevation ≥ 5 the upper limit of normal did not differ between the 2 groups. There was no between-group difference in the new onset of diabetes mellitus (Table 3). Study drug discontinuation was slightly but significantly more frequent in the high-dose group than in the low-dose group (9.8% and 8.1%; $P<0.001$).

DISCUSSION

The main finding in the present study was that cardiovascular events were significantly reduced by high-dose (4 mg/d) compared with low-dose (1 mg/d) pitavastatin therapy in Japanese patients with stable CAD.

REAL-CAD is the largest-ever trial of more versus less statins, and the first trial of this type conducted in Asia. The results from the present trial were fully consistent with the results of the TNT trial (Treating to New Targets) comparing atorvastatin 80 mg with atorvastatin 10 mg in patients with stable CAD, which demonstrated that higher-dose statin therapy was associated with lower risk for cardiovascular events.¹¹ The magnitude of relative risk reduction for the primary end point in the present study was comparable to that seen in European and North American trials of more versus less statins, suggesting that more intensive statins therapy could also be beneficial in Japanese patients.^{10–14} However, absolute risk reduction in the present study was substantially smaller than that observed in the TNT trial, reflecting the overall low event rate in Japanese patients. The very low level of hsCRP in this study is consistent with findings from previous Japanese studies^{33,34} and further reflective of the lower cardiovascular risk in Japanese patients with stable CAD.

REAL-CAD is a pragmatic physician-initiated trial exploring the optimal dose of statins for patients with established stable CAD within the range of approved doses in Japan. Despite current guidelines recommendations, rates of use of high-intensity statin therapy (atorvastatin 40/80 mg, rosuvastatin 20/40 mg) in patients with established CAD have been reported to be low in Asia (0%–25%).^{17–19} It is important to note that the statin dose in the high-dose group (pitavastatin 4 mg/d) in this study is equivalent to atorvastatin 20 mg/d in terms of LDL-C lowering, indicating that high-dose pitavastatin therapy in this study is what is generally considered moderate-intensity statin therapy in the international medical community. Most of the doses of high-intensity statin therapy defined in the American College of Cardiology/American Heart Association guideline are not approved in Japan. Furthermore, maximum approved doses of statins are prescribed very infrequently in Japan, even for secondary prevention. The mean LDL-C before the run-in period was 93 mg/dL with 91% of patients taking statins, which decreased to 88 mg/dL after the run-in period on pitavastatin 1 mg. This minimal decrease in LDL-C during the run-in period suggests that the standard of care in Japan was low-intensity statin therapy, highlighting the results of the present study as practice changing. The present study clearly demonstrated that, even in a dose range lower than the dose levels defined as high-intensity statin therapy, the higher statin dose was associated with greater protection from cardiovascular events than the lower statin dose. Furthermore, the favorable effect of high-dose pitavastatin was observed regardless of the baseline LDL-C level dichotomized as ≥ 95 and <95 mg/dL.

The present study also suggested the mortality benefit with high-dose relative to low-dose pitavastatin. We are conservative about placing too much emphasis on the observed mortality benefit because the present study did not have adequate power for evaluating the

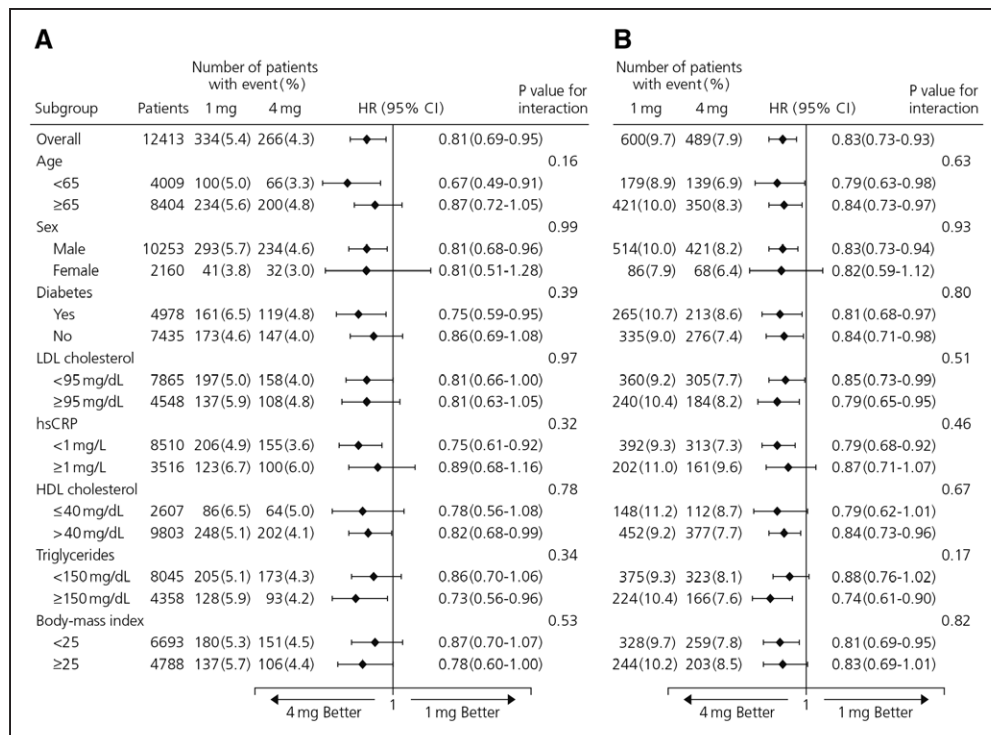


Figure 4. Subgroup analyses of the effects of high- vs low-dose pitavastatin for the primary end point and for a secondary composite end point (primary end point plus coronary revascularization) in the prespecified subgroups.

A and **B**, Subgroup analysis for the primary end point and for a secondary composite end point, respectively. Numbers of patients with event were summarized per subgroup within each treatment. Hazard ratios (HRs) were calculated within each subgroup level for the treatment effect of pitavastatin 4 mg relative to pitavastatin 1 mg. The *P* value was derived from an interaction test between the subgroup factors and treatment effect of pitavastatin 4 mg relative to pitavastatin 1 mg. Horizontal bars indicate 95% confidence intervals (CIs). Coronary revascularization as a component of the secondary composite end point excluded target-lesion revascularization for lesions treated at the time of prior percutaneous coronary intervention. HDL indicates high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; and LDL, low-density lipoprotein.

mortality difference and we cannot rule out the possibility of chance in this nonhierarchical multiple comparison for secondary end points. Furthermore, no single previous trials of more versus less statins has demon-

strated mortality benefit. However, the present study is the largest-ever trial of more versus less statins, and its results appear to favor high-dose pitavastatin from the perspective of mortality. This study thus suggests

Table 3. Adverse Events and Laboratory Test Abnormalities

Event	Pitavastatin 1 mg (n=6428), n (%)	Pitavastatin 4 mg (n=6390), n (%)	P Value
Adverse events			
Rhabdomyolysis*	1 (0.0)	2 (0.0)	0.62
Muscle complaints	45 (0.7)	121 (1.9)	<0.001
Gallbladder-related events	2 (0.0)	1 (0.0)	1.0
Cholecystectomy	0 (0.0)	0 (0.0)	
New onset of diabetes mellitus†	279 (4.3)	285 (4.5)	0.76
Psychiatric disorders	2 (0.0)	3 (0.0)	0.69
Laboratory test abnormalities			
Elevation of alanine aminotransferase, aspartate aminotransferase, or both ≥3 upper limit of normal range	174 (2.7)	187 (2.9)	0.46
Elevation of creatine kinase ≥5 upper limit of normal range	40 (0.6)	42 (0.7)	0.83

*Rhabdomyolysis was adjudicated as >10 times elevation of creatine kinase compared with upper limit of normal range and/or clinical course compatible with rhabdomyolysis.

†New-onset diabetes mellitus was defined as hemoglobin A_{1c} >6.4% at least once during follow-up in patients without diagnosis of diabetes mellitus at randomization.

that the administration of maximum tolerable doses of statins, within the range of local approval, should be the preferred statin strategy in patients with established CAD regardless of baseline LDL-C levels.

Our study has several important limitations. First, the present study was conducted as an open-label trial with its inherent limitations. However, to somewhat compensate for the open-label trial design, the primary end point was defined as not including coronary revascularization procedures because the decision for coronary revascularization is made by physicians who know the assigned treatment group. Second, the present study was terminated prematurely despite the original event-driven trial design, although we observed significant risk reduction for the primary end point. Third, final follow-up was not completed in a substantial proportion of patients, a potential limitation of physician-initiated studies that rely on voluntary efforts by the site investigators. However, the follow-up rates were comparable between the high- and low-dose groups, suggesting that the patients lost to follow-up would have affected the trial outcome in the same manner in both groups. Finally, the higher rate of study drug discontinuation and the lower rate of adherence to the study drug in the high-dose group might have nullified some of the effect of high-dose relative to low-dose therapy.

CONCLUSIONS

High-dose (4 mg/d) compared with low-dose (1 mg/d) pitavastatin therapy significantly reduced cardiovascular events in Japanese patients with stable CAD.

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High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD): A Randomized Superiority Trial

Isao Taguchi, Satoshi Iimuro, Hiroshi Iwata, Hiroaki Takashima, Mitsuru Abe, Eisuke Amiya, Takanori Ogawa, Yukio Ozaki, Ichiro Sakuma, Yoshihisa Nakagawa, Kiyoshi Hibi, Takafumi Hiro, Yoshihiro Fukumoto, Seiji Hokimoto, Katsumi Miyauchi, Tsutomu Yamazaki, Hiroshi Ito, Yutaka Otsuji, Kazuo Kimura, Jun Takahashi, Atsushi Hirayama, Hiroyoshi Yokoi, Kazuo Kitagawa, Takao Urabe, Yasushi Okada, Yasuo Terayama, Kazunori Toyoda, Takehiko Nagao, Masayasu Matsumoto, Yasuo Ohashi, Tetsuji Kaneko, Retsu Fujita, Hiroshi Ohtsu, Hisao Ogawa, Hiroyuki Daida, Hiroaki Shimokawa, Yasushi Saito, Takeshi Kimura, Teruo Inoue, Masunori Matsuzaki and Ryozo Nagai

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SUPPLEMENTAL MATERIAL

High-dose versus Low-dose Statins in Stable Coronary Artery Disease

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Leadership and Investigators

REAL-CAD Research Organization

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Independent Data Monitoring Committee: Shinichi Oikawa, Kotaro Yokote and Satoshi Morita
(Independent statistician)

Data Center: Teikyo Academic Research Center, Teikyo University, Tokyo, Japan

Inclusion and Exclusion Criteria

Inclusion Criteria

The patients who satisfy all of the following conditions at informed consent will be selected as subjects in this study and will be enrolled in the run-in period (first registration).

(1) Patients with coronary artery disease

Patients who satisfy at least one of the criteria listed in 1) through 3) below:

- 1) History of acute coronary syndrome (acute myocardial infarction or unstable angina)
- 2) Previous coronary revascularization (PCI or CABG)
- 3) Clinical diagnosis of coronary artery disease with angiographically documented coronary artery stenosis of at least 75% diameter stenosis according to the American Heart Association (AHA) classification

(2) Patients with hyper cholesterolemia

Patients who satisfy at least one of the criteria listed in 1) through 3) below:

- 1) LDL-C 140 mg/dL or above
- 2) LDL-C 100 mg/dL or above and considered by the investigator or subinvestigator to need cholesterol-lowering therapy
- 3) Already taking cholesterol-lowering drug(s)

(3) Age ≥ 20 and < 80 at the time of informed consent

(4) Have received and fully understand a comprehensive explanation regarding participation in the study, and have provided written informed consent of the participant's own free will to participate in the study.

Exclusion Criteria

Patients to whom any of the following conditions apply will be excluded from enrollment in the run-in period, even if they satisfy the inclusion criteria.

(1) Coronary revascularization has been scheduled but not yet completed

(2) Presence of active malignancy

(3) Contraindications for Livalo[®] tablets (patients with any of the following conditions)

- 1) History of hypersensitivity to any of the ingredients of Livalo[®] tablets
- 2) Serious liver disorder or bile duct obstruction
- 3) Currently under treatment with cyclosporin
- 4) Women who are pregnant, potentially pregnant, or lactating

(4) Serious heart failure (left ventricular ejection fraction $< 30\%$ or NYHA classification class III or above)

(5) Receiving dialysis

(6) Has familial hypercholesterolemia

(7) Currently participating in another clinical study

(8) Currently under treatment with a prohibited concomitant drug that cannot be discontinued

(9) Not a suitable candidate for study participation for some other reasons, in the opinion of the investigator or subinvestigator

Criteria for Exclusion for Randomization after the Run-in Period

After completion of the run-in period, the second registration will be performed.

Patients to whom any of the following conditions apply at the completion of the run-in period will not be enrolled in the follow-up period.

- (1) LDL-C 120 mg/dL or above after the completion of the run-in period
- (2) Acute coronary syndrome (acute myocardial infarction or unstable angina) during the previous 3 months
- (3) Revascularization (PCI or CABG) performed within the previous 3 months
- (4) Very poor drug-taking adherence (<50%) for the study drug (pitavastatin 1 mg/day) during the run-in period
- (5) Development during the run-in period of any events (8.1.1) corresponding to the primary endpoint of this study
- (6) Not a suitable candidate for continuing the study because of adverse events during the run-in period
- (7) Not a suitable candidate for study participation for some other reasons, in the opinion of the investigator or subinvestigator

Definition of Endpoints

Primary Endpoint

The development of any of the following events will be considered to constitute the primary endpoint.

- (1) Cardiovascular death
- (2) Non-fatal myocardial infarction
- (3) Non-fatal ischemic stroke
- (4) Unstable angina requiring emergency hospitalization

Secondary Endpoint

- (1) Composite events

- 1) Composite events for cardiovascular disease

A composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, unstable angina requiring emergency hospitalization, or non-TLR coronary revascularization based on clinical indication

TLR, target-lesion revascularization.

- 2) Composite events for coronary artery disease

A composite of coronary death, non-fatal myocardial infarction, unstable angina requiring emergency hospitalization, or non-TLR coronary revascularization based on clinical indication

- 3) Composite events for cerebrovascular disease

A composite of fatal/non-fatal stroke, hospitalization for transient ischemic attack

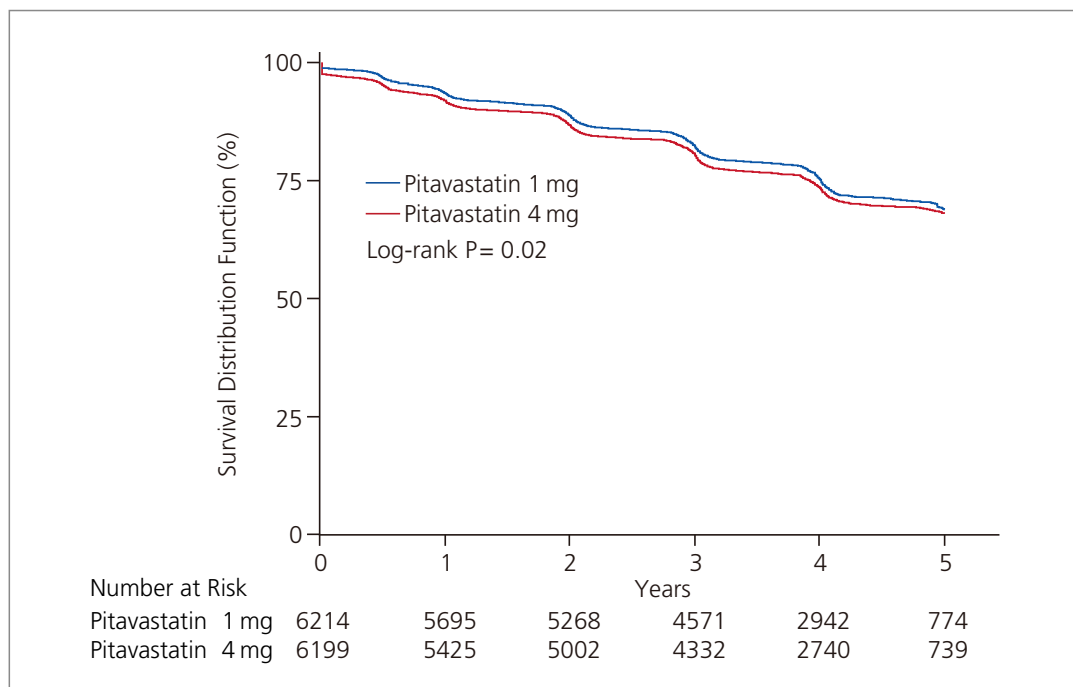
- (2) Events related to death

- 1) Death from any cause
 - 2) Cardiovascular death
 - 3) Cardiac death
 - 4) Coronary death

- (3) Events related to heart disease

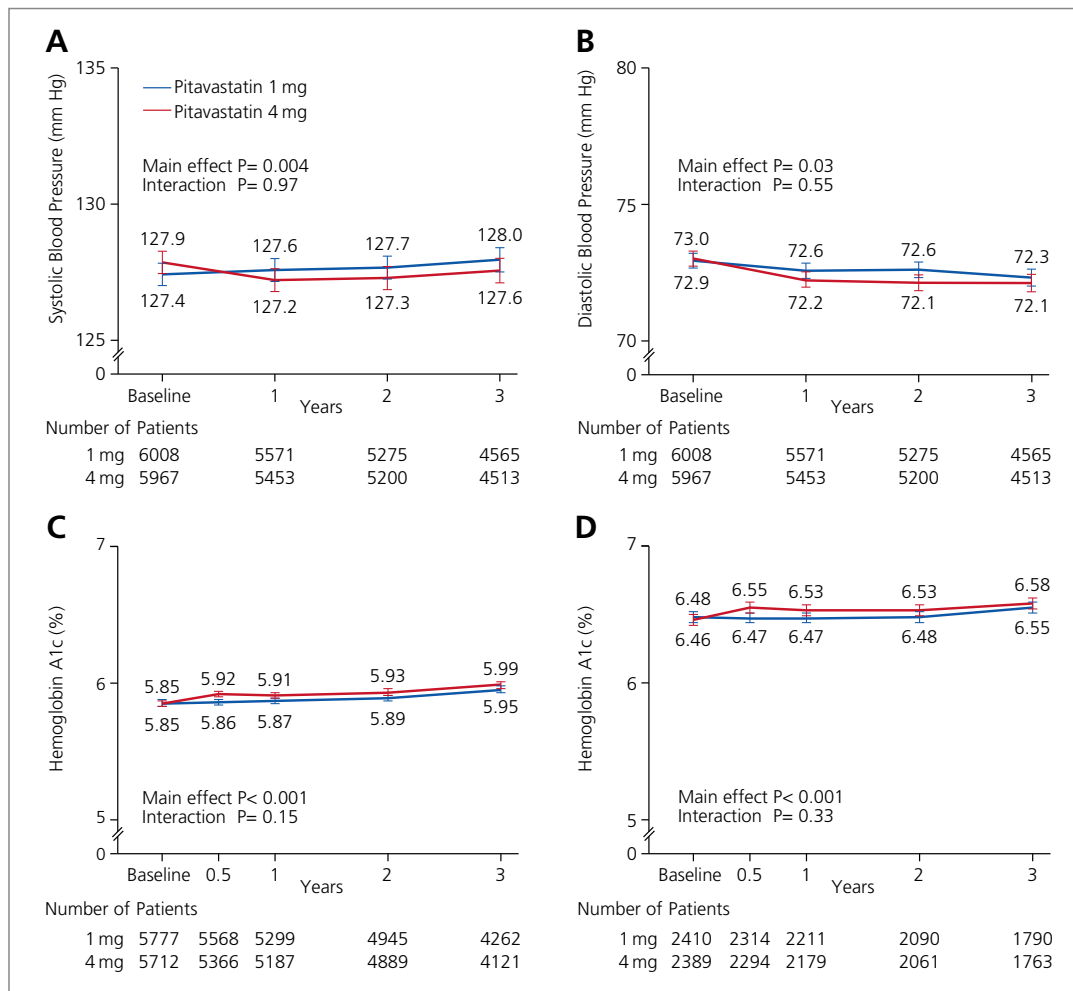
- 1) Fatal and non-fatal myocardial infarction
 - <1> Myocardial infarction not associated with procedure
 - <2> Myocardial infarction associated with procedure
 - 2) Unstable angina requiring emergency hospitalization
 - 3) Resuscitation from cardiac arrest
 - 4) Hospitalization for cardiac failure

- 5) Coronary revascularization (PCI or CABG)
 - <1> All coronary revascularizations
 - (a) non-TLR/TLR
 - (b) non-TLR
 - (c) TLR
 - <2> Coronary revascularization based on clinical indication
 - (a) non-TLR/TLR
 - (b) non-TLR
 - (c) TLR
- (4) Event related to cerebrovascular disease
 - 1) Fatal or non-fatal stroke
 - 2) Fatal or non-fatal ischemic stroke
 - <1> Ischemic stroke not associated with procedure
 - <2> Ischemic stroke associated with procedure
 - 3) Fatal or non-fatal hemorrhagic stroke
 - 4) Hospitalization for transient ischemic attack
- (5) Other events
 - 1) Surgery for aortic aneurysm or aortic aneurysm rupture
 - 2) Revascularization for peripheral artery disease (PAD)
 - 3) Carotid artery stenting (CAS) and carotid endarterectomy (CEA)
 - 4) Aortic dissection
 - 5) Deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE)
 - 6) New occurrence of malignancy
 - 7) Surgery for aortic stenosis



Supplemental Figure I. Adherence to the Study Drug Over Time

Adherence to the study drug was assessed by time-to-event analysis, in which non-adherence was regarded as the event. Non-adherence to the study drug included less than 50% intake of the study drug, discontinuation of the assigned treatment, and loss of the drug adherence data. The rate of adherence to the study drug was high in both groups, although it was slightly but significantly lower in the high-dose group than in the low-dose group.



Supplemental Figure II. Changes in Systolic Blood Pressure, Diastolic Blood Pressure, and Hemoglobin A1c Over Time

A, B, C and D show the changes over time in systolic blood pressure, diastolic blood pressure, hemoglobin A1c (all patients) and hemoglobin A1c (patients with diabetes), respectively.

P values were for the main therapeutic effect, and for the interaction effect between therapeutic effect and time.

- Dr Joseph Hill: My name is Joe Hill. I'm the Editor-in-Chief of *Circulation* and I'm very pleased today to be here today with Professor Daida from Juntendo University in Tokyo, Japan, as well as one of our associate editors, Professor Shinya Goto from Tokai University in Kanagawa, Japan. Dr. Daida is one of the senior authors on a very exciting clinical trial that we're publishing in *Circulation*. The first and largest trial comparing high-dose versus low-dose statins in Asia. Dr. Daida, would you please tell us more about the study?
- Dr Hiroyuki Daida: Yes. Thank you. The trial, called REAL-CAD, is a randomized trial. We compare high-dose statins with low-dose statins in Japanese patients with stable coronary artery disease. The number of the patients is 13,000. It's the largest trial ever comparing high-dose and low-dose statins. We found that with that reduction of the primary end point, which is a composite end point, including cardiovascular death, non-fatal MI, non-fatal stroke, and unstable angina requiring hospitalization.
- That is very exciting result because it is the largest trial ever and also the very first trial in Asia.
- Professor Shinya Goto: Congratulations, Professor Daida, for that great achievement, in the REAL-CAD trial. Could you explain a little bit about the background and that the dose of statins in Japan is generally low, and what was the reason why we kept using low-dose statins, and is care to try change the standard of care in Japan and also East Asia? Could you give a comment on those two topics?
- Dr Hiroyuki Daida: Our trial is quite similar to that of PNP trial of comparing Western extensive statin treatment and the Asia statin treatment. However, that extensive statin treatment, intensive statin treatment, is not popular in Asia, so we did that maximum clinical dose of statin, we use this dose in Japan. It is the maximum dose of statin approved in Japan.
- Dr Joseph Hill: So as I understand it, the rationale was the thinking that Asians, East Asians, are unable to tolerate high-dose statin therapy. In this case you used pitavastatin. And, in fact, what you found was there were no increase in serious adverse events in high dose patients. And, just like Caucasians, they derived considerable benefit at multiple points in atherosclerotic cardiovascular disease metrics.
- Dr Hiroyuki Daida: Actually, they didn't experience a really high-dose of statin in Japan so government approval is up to 4 mg of pitavastatin, a dose of that about 20.
- Dr Joseph Hill: So, this is not what we would call high-intensity statin therapy but nonetheless, there was a dramatic benefit including an all-cause mortality, irrespective of the starting LDL level at the beginning of the trial?

- Dr Hiroyuki Daida: That is right. We found that the effect is similar that the patient, the LDL is greater than 95 or less than 95. So, the effect is independent of the basal based on LDL level.
- Professor Shinya Goto: The one thing, very exciting just like Joe mentioned, all cause of mortality, especially known cardiovascular caused mortality reduced with the use of high-intensive care of the statin. If any kind of speculation, what is the cause, reduce the inflammation or maybe reduce cancer, something like that. They have any kind of advance to an analysis?
- Dr Hiroyuki Daida: We didn't have further analysis but we are not so keen to emphasis the total mortality because maybe that is a chance of the effect but this is the largest trial, so the result is really exciting in this kind of aspect.
- Dr Joseph Hill: So, I would reiterate Shinya's congratulations. This is a monumental piece of work. The largest clinical trial comparing high dose versus low dose statin. The largest ever. The first in Asia. You found a benefit that makes total sense across what we know from other trials and this will change practice. Your work, I believe, will change the way patients with atherosclerotic cardiovascular disease is handled in Japan.
- Dr Hiroyuki Daida: Yes, actually the current guideline in Japan for the secondary condition. The condition is LDL less than 100 and for the really high-risk secondary condition listed seventh. We didn't recommend high-dose statin initially, so, this trial result is kind of like this, changing.
- Dr Joseph Hill: I can't resist asking, what comes next? What's your next project?
- Dr Hiroyuki Daida: Maybe we need to have a further reduction of LDL. We have another drug, other potent drug recently. We need to investigate all of the new drug such as PCSK9 inhibitor in secondary prevention.
- Professor Shinya Goto: That's wonderful. Do you have any time to extend observation of the trial? I think the trial is relatively still superior as compared to the global long-standing trial. Really, that's fine, that effect of statin on the cholesterol and even it's different from Japan and other regions of the world. There ought to be intriguing thing, I would like to know, what are you waiting to extend that observation now?
- Dr Hiroyuki Daida: Fortunately, we do not intend to extend the follow-up. The whole thing is about four years but we do not plan to extend. We will further analyze the data for some group and our kind of CRP and effect of the baseline.
- Dr Joseph Hill: Lots of secondary analysis underway, undoubtedly. Let me thank both of you for being here, Professor Daida and Professor Goto, I congratulate you again. It's not often that you make a practice-changing intervention in modern-day

medicine. I salute you and we are honored and thrilled to publish your outstanding work in *Circulation*. Thank you both.

Dr Hiroyuki Daida: Thank you very much.

Professor Shinya Goto: Thank you very much.