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# Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS)

## — Rationale and Design —

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**Background** Many trials have shown that 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors reduce the incidence of cardiovascular events and mortality. One method of decreasing the incidence of cardiovascular events could be to reduce the progression of coronary atherosclerosis, and a recent study found that atorvastatin can cause coronary plaque to regress. To generalize this finding, using conventional HMG-CoA reductase inhibitors at many Japanese centers, randomized trials of pitavastatin and atorvastatin will be conducted with patients with acute coronary syndrome (ACS).

**Methods and Results** Patients with ACS who have undergone successful percutaneous coronary intervention under intravascular ultrasound guidance will be studied. They will be randomly allocated to pitavastatin or atorvastatin groups and followed up for 8–12 months. The primary endpoint will be the percent change in coronary plaque volume, and secondary endpoints will include absolute changes in coronary plaque volume, serum lipid levels and inflammatory markers. The safety profile will also be evaluated.

**Conclusions** This study will examine the ability of HMG-CoA reductase inhibitors to regress coronary plaque in Japanese patients with ACS and the findings should help to improve the prognosis of such patients and clarify the involved mechanisms. (*Circ J* 2006; **70:** 1624 – 1628)

**Key Words:** Acute coronary syndrome; Atherosclerosis; HMG-CoA reductase inhibitors; Intravascular ultrasound; Plaque

Many large-scale clinical trials have shown that 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors reduce the incidence of cardiovascular events[1–8] The relationship between low-density lipoprotein (LDL)-cholesterol (C) level and cardiovascular event frequency is linear, and an alternative strategy is reducing LDL-C to lower the cardiovascular event rate[7,8] Accordingly, current US guidelines (3rd Report of the U.S. National Cholesterol Education Program) suggest that the aim of treatment should be a LDL-C level <1.8 mmol/L (70 mg/dl) after acute coronary syndrome (ACS)[9] In the Japanese statin trial the incidence of coronary events in hypercholesterolemic patients was strongly correlated with the level of serum cholesterol[10] and the 2002 Guidelines for Diagnosis and Treatment of Atherosclerotic Diseases have established the goal of LDL-C management as <100 mg/dl in patients with coronary heart disease[11] However, no clinical trials have supported the notion that LDL-C level <100 mg/dl reduces the risk of recurrent cardiovascular events in Japanese survivors of ACS episodes.

Although reducing cardiovascular morbidity and mortality are therapeutic goals for patients with hypercholesterolemia, clinical trials that can accurately detect treatment effects using an active comparator are essentially very large and require long-term follow-up. Surrogate endpoints might provide an alternative opportunity to demonstrate efficacy in a relatively small sample size with a short follow-up. Because progressive atherosclerosis is the underlying basis of cardiovascular disease, whether or not aggressive lipid-lowering therapies, including HMG-CoA reductase inhibitors, have substantial beneficial effects on this process should be determined.

Imaging studies of coronary plaque have contributed considerably to understanding the benefits of intensive lipid-lowering therapies. The Low Density Lipoprotein-Apheresis Coronary Morphology and Reserve Trial (LACMART) has shown that aggressive lipid-lowering therapy using LDL-apheresis induces the regression of coronary atherosclerotic plaque in patients with familial hypercholesterolemia, as evaluated by intravascular ultrasound (IVUS) imaging[12] The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial found that an intensive lipid-lowering strategy using atorvastatin (80 mg/day) reduced the progression of atherosclerosis compared with moderate treatment using pravastatin (40 mg/day)[13] However, 80 mg/day of atorvastatin does not facilitate plaque regression. An IVUS assessment in the setting of aggres-

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**Table 1 Inclusion Criteria**

- *Patients giving written consent by their own volition after being provided sufficient explanation for participation in this clinical trial.*
- *Patients 20 years or older at the time of their consent.*
- *Patients with hypercholesterolemia as defined by any of the following criteria: (1) TC ≥220 mg/dl; (2) LDL-C ≥140 mg/dl; (3) cholesterol-lowering treatment is necessary in accordance with the investigator's judgement when LDL-C ≥100 mg/dl or TC ≥180 mg/dl.*
- *Patients who have been diagnosed with acute coronary syndrome.*
- *Patients with successful PCI by IVUS guidance.*
- *Patients with coronary plaques (≥500 μm in thickness or 20% or more in % plaque) at ≥5 mm from the previously treated area in the same branch of coronary artery.*

*TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound.*

**Table 2 Exclusion Criteria**

- *Patients with bypass graft or in-stent restenosis at the site of PCI.*
- *Patients who have undergone previous PCI on the lesion site where the evaluation of coronary plaque volume is planned.*
- *Patients who have plaque in a non-culprit site on the PCI vessel and might undergo PCI during the treatment period.*
- *Patients receiving lipid-lowering drugs (statins, fibrates, probucol, nicotinic acid or cholesterol absorption inhibitors).*
- *Patients with familial hypercholesterolemia.*
- *Patients with cardiogenic shock.*
- *Patients receiving cyclosporine.*
- *Patients with any allergy to pitavastatin or atorvastatin.*
- *Patients with hepatobiliary disorders.*
- *Pregnant women, women suspected of being pregnant, or lactating women.*
- *Patients with renal disorders or undergoing dialysis.*
- *Patients who are ineligible in the opinion of the investigator.*

*Abbreviation see in Table 1.*

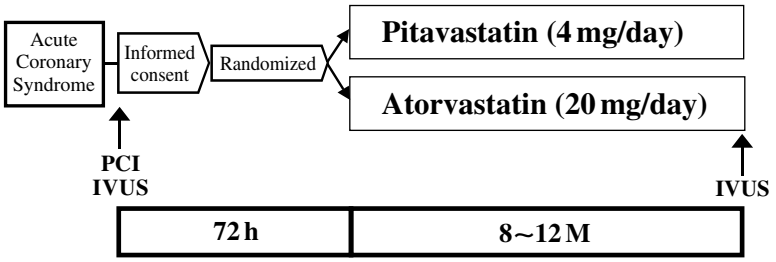


Fig 1. Protocol. PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound.

sive lipid-lowering therapy with HMG-CoA reductase inhibitors was conducted in the Japanese Early Statin Treatment in Patients with Acute Coronary Syndrome (ESTABLISH) study, which demonstrated that 20 mg/day of atorvastatin reduces coronary plaque![14] This finding suggests that aggressive lipid-lowering therapy with HMG-CoA reductase inhibitors could reduce unstable coronary plaques in ACS, but this relatively small trial was conducted at a single center and its global impact remains unknown.

Pitavastatin is a HMG-CoA reductase inhibitor with powerful lipid-lowering effects that is commonly used in Japan. Its ability to lower LDL-C is comparable to that of atorvastatin and it also enhances high-density lipoprotein (HDL)-C![15,16] Moreover, pitavastatin is not metabolized by the cytochrome P450 3A4 pathway, which is the major metabolic pathway of atorvastatin![17] Recent reports have shown that pitavastatin has pleiotropic effects; it reduces the inflammatory response![18] and the generation of reactive oxygen species![19] improves endothelial function![20] increases nitric oxide production![21] inhibits cell adhesion![22] attenuates smooth muscle cell contraction![23] increases thrombomodulin expression![24] enhances angiogenesis![25] and promotes apolipoprotein (apo) A-I production![26] However, its clinical effect on coronary plaque volume has not yet been investigated in Japan. Thus, the Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) trial will evaluate the effects of HMG-CoA reductase inhibitors with powerful lipid-lowering effects on coronary plaque regression in patients with ACS. The study will also assess whether or not the efficacy of pitavastatin is inferior to atorvastatin for plaque reduction.

## Methods

*Study Design*

JAPAN-ACS will be a randomized non-blinded parallel group study. Patients who satisfy all criteria for inclusion will be enrolled after having undergone successful percutaneous coronary intervention (PCI) under IVUS guidance to treat an episode of ACS (Table 1). Patients who satisfy any of the exclusion criteria (Table 2) will not be enrolled. The included patients will give written informed consent and then be randomly allocated to receive either pitavastatin (4 mg) or atorvastatin (20 mg) daily (Fig 1). These doses were selected based on the results of the ESTABLISH study in which 20 mg/day of atorvastatin significantly reduced coronary plaque volume in patients with ACS![14]

The pitavastatin dosage of 4 mg/day causes the same LDL-C-lowering effect as 20 mg/day of atorvastatin[15,16] The randomization will be stratified by diabetes mellitus, gender and total cholesterol (TC) level. The supervising physician will administer the allocated drugs within 72 h after PCI. The participants will continue taking the allocated drugs until the end of study, or when certain endpoints are met, including death, any cardiovascular event, any adverse event or discontinued participation in the study. Investigators will follow up the participants for 8–12 months at 36 centers, and will conduct medical examinations, blood testing, IVUS and coronary angiography (CAG). Patient enrollment is planned for between November 1, 2005 and October 31, 2006 and the enrollment period may be extended if necessary. This study has been registered at clinicaltrials.gov (NCT00242944), according to the statement of the International Committee of Medical Journal Editors:[27]

*Endpoints*

The primary endpoint will be the percent change in coronary plaque volume. Secondary endpoints include (1) absolute change from baseline in coronary plaque volume, (2) absolute and percent changes in minimal lumen diameter (MLD) and %stenosis at the site of lesion where the coronary plaque volume is evaluated, (3) absolute and percent changes in serum lipids and apolipoproteins (TC, LDL-C, triglyceride (TG), HDL-C, $HDL_2$-C, $HDL_3$-C, remnent lipoprotein-C, small dense LDL, non-HDL-C, LDL-C/HDL-C, apoA-I, apoB, apoE, apoB/apoA-I, malonyldialdehyde (MDA)-LDL, phospholipid and lipoprotein(a)), (4) absolute and percent changes in inflammatory markers (high sensitive C-reactive protein (hsCRP), pertussis toxin (PTX3)) and white blood cell count, (5) absolute and percent change in the coronary plaque area at the site of PCI, (6) absolute and percent changes in MLD and %stenosis at the site of PCI, (7) major adverse cardiovascular event (MACE; defined as cardiac death, Q or non-Q wave myocardial infarction, PCI or coronary artery bypass grafting), (8) death, and (9) any adverse incidents including changes in laboratory values.

*Safety Monitoring*

Safety will be evaluated by regular medical examination and laboratory tests at 1, 3, and 8–12 months after enrollment. The Event Assessment Committee will evaluate MACE and any other adverse events.

*Sample Size Calculation*

Because the effect of pitavastatin on coronary plaque volume has not been studied, we calculated the sample size based on the assumption that the effect of pitavastatin on the regression of coronary plaque volume is not inferior to that of atorvastatin. The % change in coronary plaque volume in patients with ACS determined by the ESTABLISH study was –13.1±12.8% (SD) in an atorvastatin group and 8.7±14.9% in a control group![14] We assumed that the mean and standard deviation of the % change in coronary plaque volume in patients receiving pitavastatin were equal to those of atorvastatin reported in the same study![14] Based on the standard deviation in the atorvastatin group, we established a non-inferiority margin of 5%. Accordingly, we calculated that groups of 150 participants with an $\alpha$ level of 5%, 80% power and a dropout rate of 30% would provide meaningful data.

*Data Management*

A data management center was established at the Research Institute for Production Development, which conducts patient enrollment, randomization and data follow-up in cooperation with the Department of Cardiovascular Medicine at Kyoto University Graduate School of Medicine. Patient information, blood samples, and IVUS images will be coded with a study identification number, and the key code for individual identification will remain blinded. Serum lipids, apolipoproteins and hsCRP will be measured at SRL Co, Ltd and PTX3 will be measured at Perseus Proteomix Co Ltd. IVUS images will be analyzed at the Division of Cardiology, Department of Medicine and Clinical Science at Yamaguchi University Graduate School of Medicine. CAG images will be analyzed at the Department of Cardiology, Juntendo University School of Medicine. An independent experienced investigator who is unaware of the patient groups will perform the quantitative IVUS analysis. Baseline and follow-up IVUS images will be reviewed together on a display, and target segments will be selected. One target segment will be determined at a non-PCI site (>5 mm proximal or distal to the PCI site) with a reproducible index side branch on the PCI vessel. The quantitative coronaty angiography analysis will also be performed by a single independent reviewer.

*Statistical Analysis*

An independent statistician with full access to the data will conduct all statistical analyses. The % change in coronary plaque volume after the 8–12 month study will be compared between groups by analysis of variance with adjustment for gender, presence of diabetes mellitus and TC level. The 2-sided 95% confidence interval will be calculated for the difference in drug effects ($\mu_p - \mu_a$) where $\mu_p$ and $\mu_a$ represent mean % change in coronary plaque volume in the pitavastatin and atorvastatin groups, respectively. Remaining within a 5% upper limit of confidence interval would confirm that pitavastatin is not inferior to atorvastatin. Similarly, not exceeding a 0% upper limit of confidence interval would indicate that pitavastatin is superior to atorvastatin.

General linear models will be used to assess relationships between the absolute change in coronary plaque volume and serum lipid level, and the % change in coronary plaque volume and serum lipid level at 8–12 months. Such models will also be used to evaluate relationships between inflammatory markers (hsCRP and PTX3) at 8–12 months, changes in coronary plaque volume and the effects of groups on changes in HDL-C.

One-sample t-tests will assess the absolute and % changes in serum lipid levels and inflammatory markers during the study period. General linear models will include the following covariates: drug, gender, age, history of coronary artery disease, hypertension, diabetes mellitus, family history of coronary artery disease, smoking status, LDL-C at baseline and HDL-C at baseline.

The number of adverse events will also be assessed to determine a safety profile. Subgroup and other analyses will also be conducted as necessary. Interim analyses have not been planned. The significance level will be 5% 2-sided (2.5% one-sided) and all statistical analyses will be performed using the SAS System Release 8.2 or SPLUS Version 7.0.

*Ethical Considerations and the Role of Funding Source*

This study will be conducted in accordance with the 'Declaration of Helsinki' established by the World Medical Association, the 'Ethical Principles in Clinical Studies' published by the Ministry of Health, Labor and Welfare of Japan and with the approval of the institutional review boards of each participating institution. The study will be explained to patients who meet the criteria for inclusion and written informed consent to participate will be obtained.

The Japan Heart Foundation supports the concept for this study and the funding source will not play any role in the design, performance, or reporting of the study, or in the decision to submit the findings for publication.

## Conclusion

The ESTABLISH study has shown that aggressive lipid-lowering therapy with 20 mg/day of atorvastatin reduces coronary plaque![14] The JAPAN-ACS study will determine if the results from the ESTABLISH study are reproducible at multiple centers using other HMG-CoA reductase inhibitors and should also confirm the utility of aggressive lipid-lowering therapy in patients with ACS in Japan.

In 2005 Tani et al found that plaque regression correlated with a decrease in MDA-LDL and an increase in HDL-C levels in 75 patients with coronary artery disease patients who received pravastatin[28] In the same year Satoh et al indicated that fasting triglyceride is a significant risk factor for coronary artery disease among middle-aged Japanese men[29] and Hong et al demonstrated that the hsCRP level is associated with neointimal hyperplasia and restenosis after successful coronary artery stenting[30] Evaluation of the effect of changes in serum lipids, including LDL-C, HDL-C, TG and MDA-LDL, and inflammatory markers, including hsCRP, on coronary plaque will be valuable in the JAPAN-ACS study and should clarify the mechanisms of coronary plaque regression.

In conclusion, the JAPAN-ACS study will investigate a wide range of endpoints to determine the effect of aggressive lipid-lowering therapy, the utility of 2 HMG-CoA reductase inhibitors with powerful lipid-lowering effects, and the mechanisms of coronary plaque regression in Japanese patients with ACS.

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## Appendix 1

*Research Group Organization*

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