Differences Between Rosuvastatin and Atorvastatin in Lipid-Lowering Action and Effect on Glucose Metabolism in Japanese Hypercholesterolemic Patients With Concurrent Diabetes
– Lipid-Lowering With Highly Potent Statins in Hyperlipidemia With Type 2 Diabetes Patients (LISTEN) Study –

Hisao Ogawa, MD, PhD; Kunihiko Matsui, MD, PhD; Yoshihiko Saito, MD, PhD; Seigo Sugiyama, MD, PhD; Hideaki Jinnouchi, MD, PhD; Masahiro Sugawara, MD, PhD; Izuru Masuda, MD, PhD; Hisao Mori, MD, PhD; Masako Waki, MD, PhD; Minoru Yoshiyama, MD, PhD; Hirotaka Watada, MD, PhD

Background: Little is known about the differences between standard-dose statins effects on glucose level and lipids in Japanese patients with diabetes mellitus (DM).

Methods and Results: The 1,049 patients were randomly assigned to either the rosuvastatin group or atorvastatin group. There were no significant differences between the 2 groups in the effect on non-high-density lipoprotein cholesterol (non-HDL-C) and HbA1c at 12 months. However, physicians tended to switch to more intensive therapy for DM in the atorvastatin group.

Conclusions: Rosuvastatin 5 mg and atorvastatin 10 mg have a similar lowering effect on non-HDL-C, but might be different in terms of adverse effect on glucose levels.

Key Words: Hypercholesterolemia; Statins; Type 2 diabetes mellitus

The clinical benefit of preventing cardiovascular events by using statins in hypercholesterolemic patients is well established.1,2 The benefit in hypercholesterolemic patients with diabetes mellitus (DM) has also been demonstrated in several randomized trials,3–5 but recent data showed that statins are associated with an increased risk of new-onset DM6,7 and that the risk is dose dependent.8 Some reports suggested the suppressive effect of statin on cardiovascular events outweighs the risk of DM onset.9–11 The guidelines show the rationale for statin therapy to prevent cardiovascular events based on risk stratification for each patient, which includes DM.12,13 However, few prospective, randomized, controlled studies have been conducted to investigate the effect of statin therapy on glucose levels in patients with DM, although such data would greatly contribute to decision making in the clinical setting. We conducted this study to examine the effects of statins on both glucose and lipid levels in Japanese patients with DM. The final result will be presented in a hot-line session of the ESC congress 2014.

Methods
This study was a 12-month multicenter open-label randomized, comparative study. The protocol was approved by the institutional review board. All patients provided written informed consent.

The study included hypercholesterolemic patients with type
2 DM whose HbA1c (Japan Diabetes Society [JDS]) was <7.0\% (or <7.4\%: National Glycohemoglobin Standardization Program [NGSP]). Patients were excluded if they had received rosuvastatin or atorvastatin before registration. Patients were randomly assigned to the rosuvastatin 5 mg group or the atorvastatin 10 mg group at registration.

The primary endpoints were the percentage change in non-high-density lipoprotein cholesterol (non-HDL-C) and the change in HbA1c. Secondary endpoints were changes in other lipids, glucose metabolism parameters, and any intensification of DM treatment (ie, drugs were added and/or increased for DM), which was assessed independently by 2 investigators. The original agreement on $\kappa$ score was 0.6316, which was fairly good, and discrepancies were fixed by direct discussion.

**Figure 1.** Percent change in non-HDL-C (A) and change in HbA1c (B). The analyses were performed using repeated measures ANOVA for overall comparison between the 2 statin treatment groups. The unpaired t-test adjusted by Holm's method was used for intergroup comparison to avoid multiplicity at multiple time points. Non-HDL-C, non-high-density lipoprotein cholesterol.

**Figure 2.** Cumulative Kaplan-Meier estimates of the incidence of the patients who were switched to more intensive therapy for diabetes mellitus. The atorvastatin group had therapy intensified more often than the rosuvastatin group during the study period (P=0.05). CI, confidence interval.
Statistical Analysis
The 2-way repeated measures ANOVA was used to compare the groups for changes in lipid profiles and glucose metabolism parameters from baseline to each assessment time. The unpaired t-test adjusted by Holm’s method was used for intergroup comparison to avoid multiplicity at multiple time points. A log-rank test was used to compare intensification of DM treatment between the groups.

Results
A total of 1,049 patients were enrolled and randomized to the rosuvastatin or atorvastatin group from March to September 2012 at 132 institutions in Japan; 514 patients in the rosuvastatin group and 504 patients in the atorvastatin group were included in the full analysis set. There were no significant differences between the groups at baseline (Table S1).

Lipid Profiles and Glucose Levels
Non-HDL-C showed a significant reduction in both groups (−32.86% in the rosuvastatin group and −31.01% in the atorvastatin group at 12 months) without a significant difference between groups (Figure 1A). Low-density lipoprotein cholesterol levels were also decreased at 12 months: −34.79% in the rosuvastatin group and −32.78% in the atorvastatin group (Figure S1).

The changes in HbA1c were 0.11 in the rosuvastatin group and 0.12 in the atorvastatin group (Figure 1B). There was a significant difference at 6 months even after adjustment for multiple comparisons, but not significant difference between groups throughout the study period. Other glucose metabolism parameters did not show significant differences between groups (Figure S2). The cumulative incidence of intensification of DM treatment is shown in Figure 2. During the study period, 45 subjects in the rosuvastatin group and 64 subjects in the atorvastatin group were treated with increased DM therapy (Table S2). The hazard ratio was 1.46 (95% confidence interval 1.00–2.14) (Figure 2).

Safety
Adverse effects occurred in 4.5% of the rosuvastatin group and 5.9% of the atorvastatin group. There were no cases of rhabdomyolysis or of liver function enzyme elevation greater than 3-fold the upper limit of normal.

Discussion
There were no significant changes in non-HDL-C or HbA1c in either group. However, there were differences in the effects on glucose levels and treatment decisions for DM. A meta-analysis has shown that statin therapy is associated with an increased risk of developing DM, but did not show any obvious differences among the individual statins, which are classified as hydrophilic or lipophilic. Takaguri et al reported that lipophilic but not hydrophilic statins significantly affected glucose uptake by adipocytes, and MUSASHI-AMI showed that cardiovascular events tended to be fewer with hydrophilic statins.

To complement the results from previous studies, our results should be interpreted that the choice of statin be considered not only on the basis of potency of cholesterol-lowering effect but also glucose metabolism. In our study results, rosuvastatin and atorvastatin showed different patterns of change in HbA1c. The atorvastatin group tended to be changed to more intensive DM therapy. At 6 months, HbA1c levels showed a statistically significant difference between groups, and that would have influenced physicians’ behavior to change the intensity of DM treatment. Consequently, the overall change in HbA1c did not reach statistically significant difference. However, our results suggested rosuvastatin might be preferable to atorvastatin in this study population.

There are several limitations to this study. Firstly, we compared laboratory data mainly as the outcome; in addition, the long-term outcome is uncertain. Moreover, the differences in glucose levels between the 2 statins were determined by the changes in HbA1c levels, in addition to the treatment intensity for DM. Secondly, our study used small dosages based on the Japanese regulation, so the results might underestimate the effects of statins. Besides, this was an open-label study in which the possibility of bias cannot be entirely denied. However, both groups were treated aggressively for DM, as the results for HbA1c level at 12 months were similar between groups, although they were different at 6 months. We believe our findings would be close to the real clinical setting.

Conclusions
Rosuvastatin 5 mg and atorvastatin 10 mg have a similar lowering on non-HDL-C, but might be different in terms of adverse effect on glucose levels.

Funding Sources
LISTEN was funded by the investigator-sponsored study program of AstraZeneca.

Disclosures
H.O. has received grants from the Japan Heart Foundation, and has received research supports or honoraria or both from Astellas Pharma Inc, AstraZeneca KK, Bayer Yakuhin, Ltd, Boehringer Ingelheim Japan, Inc, Bristol-Myers Squibb Company, Chugai Pharmaceutical Co, Ltd, Daichi Sankyo Company, Limited, Dainippon Sumitomo Pharma Co, Ltd, Kowa Company, Ltd, MSD KK, Novartis Pharma KK, Otsuka Pharmaceutical Co, Ltd, Pfizer Japan Inc, Sanofi KK, and Takeda Pharmaceutical Company Limited.

Y.S. is an adviser at Ono Pharmaceutical Co, Ltd. Y.S. has a clinical commission for an advisor from Ono Pharmaceutical Co, Ltd. Y.S. has received research supports or honoraria or both from Astellas Pharma Inc, AstraZeneca KK, Daiichi Sankyo Company, Limited, Kyowa Hakko Kirin Co, Ltd, Mitsubishi Tanabe Pharma Corporation, MSD KK, Novartis Pharma KK, Otsuka Pharmaceutical Co, Ltd, Pfizer Japan Inc, Shionogi & Co, Ltd, St. Jude Medical Japan Co, Ltd, and Takeda Pharmaceutical Company Limited. Y.S. has endowed departments by MSD Co, Ltd.

M.Y. has received research supports or honoraria or both from Astellas Pharma Inc, Boehringer Ingelheim Japan, Inc, Bristol-Myers Squibb Company, Daiichi Sankyo Company, Limited, Dainippon Sumitomo Pharma Co, Ltd, Eisai Co, Ltd, GlaxoSmithKline KK, Kissei Pharmaceutical Co, Ltd, Kyowa Hakko Kirin Co, Ltd, Mochida Pharmaceutical Co, Ltd, MSD KK, Otsuka Pharmaceutical Co, Ltd, Pfizer Japan Inc, Sanofi KK, and Teijin Pharma Limited.

H.W. has received research supports or honoraria or both from Astellas Pharma Inc, AstraZeneca KK, Boehringer Ingelheim Japan, Inc, Bristol-Myers Squibb Company, Daiichi Sankyo Company, Limited, Dainippon Sumitomo Pharma Co, Ltd, Eli Lilly Japan KK, Johnson & Johnson KK, Kissei Pharmaceutical Co, Ltd, Kowa Company, Ltd, Kyowa Hakko Kirin Co, Ltd, Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical Co, Ltd, MSD KK, Novartis Pharma KK, Novo Nordisk Pharma Ltd, Ono Pharmaceutical Co, Ltd, Pfizer Japan Inc, Sanofi KK, and Teijin Pharma Limited.



References
1. Miyauchi K, Daida H, Morimoto T, Hiro T, Kimura T, Nakagawa Y, et al. Reverse vessel remodeling but not coronary plaque regression could predict future cardiovascular events in ACS patients with intensive statin therapy: The extended JAPAN-ACS study. Circ J 2012; 76: 825–832.
2. Natsuki M, Furukawa Y, Morimoto T, Nakagawa Y, Ono K, Kaburagi S, et al. Intensity of statin therapy, achieved low-density lipoprotein cholesterol levels and cardiovascular outcomes in Japanese patients after coronary revascularization: Perspectives from the
appendices