Assessment of Lipophilic vs. Hydrophilic Statin Therapy in Acute Myocardial Infarction – ALPS-AMI Study –

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Background: Statins reduce the incidence of cardiovascular events, but no randomized trial has investigated the best statins for secondary prevention. We compared the efficacy of hydrophilic pravastatin with that of lipophilic atorvastatin in patients with acute myocardial infarction (AMI).

Methods and Results: A prospective, multicenter study enrolled 508 patients (410 men; mean age, 66.0 ± 11.6 years) with AMI who were randomly assigned to atorvastatin (n=255) or pravastatin (n=253). The target control level of low-density lipoprotein cholesterol (LDL-C) was <100 mg/dl, and patients were followed for 2 years. The primary endpoint was the composite of death due to any cause, non-fatal myocardial infarction, non-fatal stroke, unstable angina or congestive heart failure requiring hospital admission, or any type of coronary revascularization. The primary endpoint occurred in 77 patients (30.4%) and in 80 patients (31.4%) in the pravastatin and atorvastatin groups, respectively (hazard ratio, 1.181; 95% confidence interval: 0.862–1.619; P=0.299), whereas greater reductions in serum total cholesterol and LDL-C were achieved in the atorvastatin group (P<0.001 for each). Changes in hemoglobin A1c, brain natriuretic peptide, and creatinine were not significant between the 2 regimens, and safety and treatment adherence were similar.

Conclusions: On 2-year comparison of hydrophilic and lipophilic statins there was no significant difference in prevention of secondary cardiovascular outcome.

Key Words: Acute myocardial infarction; Secondary prevention; Statin
**Table 1. Baseline Clinical Characteristics**

<table>
<thead>
<tr>
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<th>Pravastatin</th>
<th>Atorvastatin</th>
<th>P-value</th>
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<tbody>
<tr>
<td>n</td>
<td>253</td>
<td>255</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>205 (81.0)</td>
<td>205 (80.4)</td>
<td>0.856</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.7±11.7</td>
<td>66.3±11.4</td>
<td>0.822</td>
</tr>
<tr>
<td>Smoking (Brinkman index)</td>
<td>505.0±558.6</td>
<td>513.1±532.3</td>
<td>0.526</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>131.8±23.2</td>
<td>134.8±24.3</td>
<td>0.692</td>
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<tr>
<td>DBP (mmHg)</td>
<td>80.1±15.9</td>
<td>80.2±16.3</td>
<td>0.721</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>204.1±38.6</td>
<td>203.2±40.8</td>
<td>0.118</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>130.2±33.2</td>
<td>131.0±33.9</td>
<td>0.310</td>
</tr>
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<td>HDL-C (mg/dl)</td>
<td>47.6±11.4</td>
<td>48.0±12.4</td>
<td>0.260</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>142.9±114.2</td>
<td>130.8±94.3</td>
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<tr>
<td>HbA1c (%)</td>
<td>6.34±1.27</td>
<td>6.26±1.22</td>
<td>0.696</td>
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<td>Creatinine (mg/dl)</td>
<td>0.89±0.65</td>
<td>0.88±0.46</td>
<td>0.619</td>
</tr>
<tr>
<td>eGFR (ml·min⁻¹·1.73m⁻²)</td>
<td>71.2±19.6</td>
<td>70.7±20.4</td>
<td>0.629</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>142.8±215.4</td>
<td>126.7±174.7</td>
<td>0.140</td>
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<tr>
<td>Indication for PCI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>STEMI</td>
<td>203 (80.2)</td>
<td>212 (83.1)</td>
<td>0.494</td>
</tr>
<tr>
<td>Non-STEMI</td>
<td>50 (19.8)</td>
<td>43 (16.9)</td>
<td>0.494</td>
</tr>
<tr>
<td>LVEF</td>
<td>55.3±11.7</td>
<td>54.5±12.2</td>
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<td>Killip classification</td>
<td></td>
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<td>0.897</td>
</tr>
<tr>
<td>I</td>
<td>213</td>
<td>208</td>
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<tr>
<td>II</td>
<td>23</td>
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<td></td>
</tr>
<tr>
<td>III</td>
<td>3</td>
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<tr>
<td>IV</td>
<td>3</td>
<td>5</td>
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Data given as n (%), or mean±SD. BNP, brain natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol.
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Study Design
Patients were randomly allocated to receive either atorvastatin or pravastatin using a minimization approach to ensure that the 2 groups were balanced with respect to age, gender, LDL-C, and hemoglobin A1c (HbA1c). Each statin was started at 10 mg once daily, and the treatment target was to reduce LDL-C to <100 mg/dl following the Japanese Guidelines for Secondary Prevention of Myocardial Infarction (Japanese Circulation Society 2011). If the subject's LDL-C was >100 mg/dl after 4 weeks of statin treatment, the dose was increased to 20 mg daily. After 8 weeks of statin treatment, 10 mg ezetimibe was added daily if serum LDL-C still exceeded 100 mg/dl. Patients were enrolled from June 2008 to December 2010 and followed for at least 24 months, until 2013. The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. The protocol was approved by each participating site’s ethics committee, and was registered at the University Hospital Medical Information Network (UMIN000001521).

Study Definition and Endpoints
AMI was diagnosed according to the AHA/ACC guidelines. The primary endpoint was the composite of death due to any cause, non-fatal myocardial infarction (MI), non-fatal stroke, congestive heart failure requiring hospital admission, or any arrhythmic events or the presence of hemodynamic instability (hypotension, congestive heart failure, or mechanical complications following AMI).

Methods
Subjects
The Assessment of Lipophilic versus Hydrophilic Statin Therapy in Acute Myocardial Infarction (ALPS-AMI) study was a prospective, randomized, open-labeled, blinded endpoint study that recruited patients at 20 participating sites in Nagano and Niigata prefectures of Japan (Appendix). Details of the study methods, design, and sample size calculations have been published. Briefly, the inclusion criteria included: male or female, aged >20 years, serum low-density lipoprotein cholesterol (LDL-C) >70 mg/dl, written informed consent, and percutaneous coronary intervention (PCI) to treat either ST-segment elevation or non-ST-segment elevation AMI done within 96h. Exclusion criteria included planned surgery for coronary artery bypass grafting, pregnancy, active liver or renal disease, malignant disease, withdrawal of informed consent, and serious clinical trial has prospectively randomized statin type with regard to efficacy and safety in patients with AMI. Under these circumstances, this study was designed as a head-to-head comparison of the efficacy of lipophilic atorvastatin vs. hydrophilic pravastatin at clinical doses for Japanese patients with secondary prevention following AMI. We hypothesized that pravastatin likely reduces the incidence of adverse cardiac events relative to those with atorvastatin based on the MUSASHI-AMI subanalysis. This study provides new insights into the difference between lipophilic atorvastatin and hydrophilic pravastatin according to direct clinical comparison.
ary endpoint in this study included changes in laboratory parameters: serum total cholesterol (TC), LDL-C, high-density lipoprotein-cholesterol (HDL-C), triglyceride, brain natriuretic peptide (BNP), creatinine, and HbA1c concentration, which were calculated according to the National Glycohemoglobin Standardization Program. The percentage of patients who achieved the target LDL-C <100 mg/dl, and any adverse incidents were also evaluated.

Statistical Analysis

Differences between regimens for continuous variables were evaluated using unpaired t-test, and those for categorical variables were analyzed using Fisher’s exact test or chi-squared test. Time-course changes of laboratory parameters between regimens were compared using a mixed model with Bonferroni’s correction. Cumulative incidence of primary endpoints was constructed using the Kaplan-Meier method, and log-rank test was performed to compare differences between the regimens. Cox proportional hazards regression was used to calculate hazard ratio (HR) and 95% confidence interval (CI). All analysis was conducted with SPSS version 18.0 (IBM, Armonk, NY, USA), and 2-tailed with significance defined as P<0.05.

Results

A total of 528 AMI patients were recruited. After randomization, 261 and 264 patients were allocated to the pravastatin and atorvastatin groups, respectively (Figure 1). Patients were then followed up for 2 years (the follow-up rate was 95.9%) except for 8 patients in the pravastatin and 7 patients in the atorvastatin groups due to violation of the exclusion criteria, withdrawal of consent or other reasons. Mean patient age was 66.0 ± 11.6 years. Mean serum lipids for the total patient group were as follows: TC, 203.6 ± 39.7 mg/dl; LDL-C, 130.6 ± 33.5 mg/dl; HDL-C, 47.8 ± 11.9 mg/dl; and triglycerides, 136.8 ± 104.7 mg/dl. Patient background is given in Table 1. A minimization method was used to balance age, gender, LDL-C, and HbA1c, and thus patients in the 2 regimens were well-matched for baseline characteristics. No differences between regimens were observed in Killip classification or left ventricular ejection fraction, suggesting similar patient hemodynamic status in the acute phase.

Pravastatin reduced TC by 19% at 6 months (166.0 ± 2.2 mg/dl), at 12 months (165.6 ± 2.5 mg/dl), and at 24 months (165.6 ± 2.5 mg/dl). LDL-C reduction on pravastatin was 28% (94.0 ± 1.9 mg/dl) at 6 months, 31% (91.3 ± 1.9 mg/dl) at 12 months, and 29% (92.0 ± 2.0 mg/dl) at 24 months. Atorvastatin further significantly reduced lipid levels as follows: TC reduction was 26% (151.2 ± 2.0 mg/dl) at 6 months, 25% (152.6 ± 2.0 mg/dl) at 12 months, and 24% (153.8 ± 2.0 mg/dl) at 24 months. Atorvastatin further significantly reduced lipid levels as follows: TC reduction was 26% (151.2 ± 2.0 mg/dl) at 6 months, 25% (152.6 ±

Table 2. Clinical Outcome

<table>
<thead>
<tr>
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<th>Pravastatin</th>
<th>Atorvastatin</th>
<th>P-value</th>
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<tbody>
<tr>
<td>All-cause death</td>
<td>14 (5.5)</td>
<td>9 (3.5)</td>
<td>0.277</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>3 (1.2)</td>
<td>3 (1.2)</td>
<td>0.992</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (2.0)</td>
<td>4 (1.6)</td>
<td>0.728</td>
</tr>
<tr>
<td>Others</td>
<td>5 (2.0)</td>
<td>1 (0.4)</td>
<td>0.098</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>0.996</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.4)</td>
<td>0</td>
<td>0.315</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (2.0)</td>
<td>1 (0.4)</td>
<td>0.098</td>
</tr>
<tr>
<td>Revascularization (PCI, CABG)</td>
<td>51 (20.2)</td>
<td>63 (24.7)</td>
<td>0.219</td>
</tr>
<tr>
<td>Hospitalization due to HF</td>
<td>6 (2.4)</td>
<td>7 (2.7)</td>
<td>0.790</td>
</tr>
</tbody>
</table>

Data given as n (%). CABG, coronary artery bypass grafting; HF, heart failure; PCI, percutaneous coronary intervention.

Figure 3. Kaplan-Meier estimates of the incidence of (A) primary endpoints (composite of death due to any cause, non-fatal myocardial infarction, non-fatal stroke, congestive heart failure requiring hospital admission, or any type of coronary revascularization), and (B) major adverse cardiovascular events (composite of death due to any cause, non-fatal myocardial infarction, or non-fatal stroke). P-values (log-rank test) are given for comparison between the 2 regimens.
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2.2 mg/dl) at 12 months, and 25% (153.9±2.2 mg/dl) at 24 months; and LDL-C reduction was 39% (80.0±1.6 mg/dl) at 6 months, 38% (81.3±1.7 mg/dl) at 12 months, and 37% (82.5±1.7 mg/dl) at 24 months. On comparison between regimens, serum TC and LDL-C in the atorvastatin group were significantly lower than in the pravastatin group (P<0.001 for both), despite having the same treatment target for LDL-C control (Figure 2). Triglycerides were also lower in the atorvastatin group (P<0.01). No difference in HDL-C level was observed between the pravastatin and atorvastatin groups, respectively, as follows: 49.2±0.8 mg/dl and 48.8±0.8 mg/dl at 6 months, 50.4±0.8 mg/dl and 50.1±0.8 mg/dl at 12 months, and 50.4±0.8 mg/dl at 24 months (Figure 2). In addition, there were significantly more patients who required ezetimibe to achieve LDL-C <100 mg/dl at 8 weeks after primary PCI in the pravastatin group (n=48, 19%) as compared with 12 (4.7%) in the atorvastatin group (P<0.001).

The incidence of primary endpoints was similar in both regimens: a total of 77 endpoints (30.4%) in the pravastatin group, and 80 endpoints (31.4%) in the atorvastatin group (Table 2). On Kaplan-Meier analysis, the cumulative incidence of primary endpoints was similar between the 2 regimens on intention-to-treat analysis (log-rank test, P=0.2985; Figure 3A), and also on per-protocol analysis (P=0.3664). A Kaplan-Meier curve was also constructed for the incidence of major adverse cardiovascular events (composite of death due to any cause, non-fatal MI, or non-fatal stroke) and showed no difference between the 2 regimens (P=0.1150; Figure 3B). Overall HR of atorvastatin was 1.181 (95% CI: 0.862–1.619, P=0.299), indicating similar benefit for the 2 types of statins (Figure 4). Likewise, similar benefits for both regimens were seen on subgroup analysis, which compared men and women, smokers and non-smokers, patients treated with and without ezetimibe, and also patients grouped by median age, body mass index, and serum level of either LDL-C, HDL-C, or HbA1c, estimated glomerular filtration rate, high-sensitivity C-reactive protein, or BNP (Figure 4).

Moreover, none of the differences between regimens was significant for time course serum BNP, HbA1c, and creatinine during the follow-up period, and, importantly, there was no significant increase in HbA1c in either of the statin regimens (Figure 5). Although changes in BNP between the regimens was not statistically significant, in the pravastatin group there was prompt decrease in BNP at 2, 6 and 12 months after treatment. In addition, the pravastatin group had no increase in creatinine throughout the follow-up period, as compared with a modest increase in the atorvastatin group (Figure 5).

The rate of discontinuation of treatment due to adverse effects or other reasons was 2.8% in the pravastatin group and 2.4% in the atorvastatin group (P=0.7677). The major reason for discontinuation in both regimens was liver function abnormality.

Discussion

In this prospectively randomized, head-to-head comparison of the 2 statin regimens of either hydrophilic pravastatin or lipophilic atorvastatin, the main findings were as follows: (1) cu-
Serum lipid abnormalities of the enrolled patients at the onset of AMI were not remarkable (Table 1). In the recent statin era, similar serum lipid levels at the onset of acute coronary syndrome have been reported in the JAPAN-ACS and INTERHEART studies. It is noteworthy, however, that LDL-C is associated with risk of AMI among Asian subjects despite the lower baseline serum LDL-C, and moreover, early statin therapy has been of benefit in these patients with low LDL-C.

It is widely accepted that maintaining low LDL-C is associated with a lower incidence of cardiovascular events. In this study, significantly low LDL-C and TC were achieved in the atorvastatin group, but there was no significant difference in the primary endpoints between the regimens. In addition, the incidence of primary endpoints in each regimen was not dependent on lower levels of either LDL-C or TC at 6 months after treatment. Pleiotropic factors, as well as the beneficial effects of lipid control, therefore, might be involved in the similar event-free survivals of the 2 regimens. Taking these findings into consideration, pravastatin might have pleiotropic advantages in the prevention of secondary cardiovascular events beyond its LDL-C-lowering action.

Recently, pleiotropic effects of statins have been highlighted with regard to anti-inflammatory effects, antioxidant effects, and protective effects on endothelial cells, all of which may have some benefit in maintaining target organ function and specifically, potential benefits of statin treatment have been demonstrated in patients with heart failure and/or chronic kidney disease. Subgroup analysis of The Treating to New Targets (TNT) study showed that treatment with high-dose atorvastatin was associated with a significant decrease in rate of heart failure hospitalizations compared to low-dose treatment. A post-hoc analysis of the TNT trial recently showed that improvement in kidney function might be related to the beneficial effect of high-dose atorvastatin on heart failure hospitalization. In the present study, however, no definite benefit was seen with regard to change in creatinine and BNP in the atorvastatin group. In contrast, pravastatin appeared to preserve kidney function, showing no increase in serum creatinine level, as compared with the modest increase in the atorvastatin group. Interestingly, similar benefits of pravastatin on renal protection in patients with moderate chronic kidney disease have been demonstrated in a post hoc analysis of the MEGA study. These potential benefits of pravastatin were consistent with experimental data in a five-sixths nephrectomized rat model, in which pravastatin preserved renal function. Moreover, the effect of pravastatin was followed by protection against left ventricular hypertrophy in the rat model. Furthermore, BNP in patients treated with pravastatin showed a prompt decrease at 2 and 6 months after treatment in this study. Taken together, pravastatin might have advantages of both renal and cardioprotection after AMI, and thus can be considered as a first-line therapy after the onset of MI. Further clinical research is warranted to evaluate the mechanisms of cardiac and/or renal protection and the difference between statin types.

Differences between hydrophilic and lipophilic statins have been shown to be tissue-specific statin effects, because lipophilic atorvastatin and fluvastatin, but not pravastatin, also worsened stunning of the myocardium after coronary reperfusion, which was associated with reduction in tissue adenosine triphosphate. In a dog model of myocardial ischemia, lipophilic simvastatin enhanced myocardial stunning and resulted in worsening of segment shortening in the reperfused myocardium as compared with control and pravastatin. In addition, lipophilic atorvastatin and fluvastatin, but not pravastatin, also worsened stunning of the myocardium after coronary reperfusion, which was associated with reduction in tissue adenosine triphosphate. Clinically similar effects of simvastatin and pravastatin have been reported in cardiac allograft rejection and survival, and moreover, a non-randomized observational comparison of hydrophilic or lipophilic statins has demonstrated similar 1-year outcomes in patients with AMI. Although...
the mechanism of action and differential effects of each statin were beyond the scope of the present study, pravastatin demonstrated similar efficacy for secondary prevention in real clinical practice despite a lower potency for serum lipid control.

We also observed no significant difference in the primary endpoints between the presence and absence of ezetimibe in each regimen, as well as among all patients in this study (P=0.1193, log-rank test). Beneficial effects of ezetimibe have been demonstrated not only on serum oxidized cholesterol65 or stable or asymptomatic low-density lipoprotein cholesterol66 but also on clinical outcomes following elective vascular surgery67 or AMI.68 Conversely, combined therapy of ezetimibe and simvastatin showed no difference in intima-media thickness as compared with simvastatin alone;69 moreover, the use of ezetimibe led to a paradoxical increase in the carotid intima-media thickness in association with greater reduction in LDL-C.40,41 The present study was not designed to evaluate the efficacy of ezetimibe, but no disadvantage was observed in patients requiring ezetimibe to control high LDL-C under the initial statin therapy. Further studies are required to elucidate whether the addition of ezetimibe improves clinical outcome following AMI.

Finally, we assessed a possible difference in change in HbA1c, which has been a dilemma among patients requiring lipid control with statin treatment. Statin use in the general population has been associated with an increase in diabetes occurrence,12 whereas the benefits of statin outweigh the hazards in secondary prevention subjects.10,11,42 In the present study period, we observed no difference in HbA1c between the regimens and no significant changes in HbA1c in each regimen.

Study Limitations
First, the composite of primary endpoints included soft endpoints such as congestive heart failure requiring hospital admission or any type of coronary revascularization. Consequently, an exclusive conclusion could not be made on the efficacy regarding major adverse cardiovascular events. This limitation was based on the statistical power of calculation of this study, which involved a relatively small number of patients. Second, the primary endpoints included any type of coronary revascularization that could be associated with target lesion characteristics or technical details of coronary intervention. In this study, however, these procedural aspects were not evaluated. Third, the patients were exclusively Japanese, who were treated following the Japanese guidelines with relatively lower standard doses of statins compared to other countries. Fourth, the design of this study did not allow analysis of the efficacy of ezetimibe, as well as other background agents used concomitantly with statins. In addition, we could not evaluate impact of dose of each statin or ezetimibe, because these doses were not serially recorded during the study period. Finally, further research to assess the residual risks or new biomarkers predicting cardiovascular events is warranted, because abnormalities of traditional cardiovascular risk factors in the present patients were not remarkable.

Conclusions
This was the first multicenter randomized trial to compare the efficacy and safety of lipophilic atorvastatin and hydrophilic pravastatin in Japanese patients following AMI. Although control of low lipid level was achieved in the atorvastatin group, there was no significant difference between the 2 regimens in the prevention of secondary cardiovascular outcome.

Acknowledgments
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Disclosures
None.

References


Appendix

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