Effect of Early Use of Low-Dose Pravastatin on Major Adverse Cardiac Events in Patients With Acute Myocardial Infarction
—— The OACIS-LIPID Study ——

Hiroshi Sato, MD; Kunihiro Kinjo, MD; Hiroshi Ito, MD*; Atsushi Hirayama, MD**; Shinsuke Nanto, MD†; Masatake Fukunami, MD‡; Masami Nishino, MD‡; Young-Jae Lim, MD‡‡; Yoshiyuki Kijima, MD§; Yukihiro Koretsune, MD§§; Daisaku Nakatani, MD; Hiroya Mizuno, MD; Masahiko Shimizu, MD; Masatsugu Hori, MD; for the Osaka Acute Coronary Insufficiency Study (OACIS)-LIPID Study Investigators

Background It is unclear whether early initiation of low-dose pravastatin therapy can reduce the occurrence of major adverse cardiac events after acute myocardial infarction (AMI).

Methods and Results The study group comprised 353 patients with AMI who had plasma total cholesterol levels of 200–250 mg/dl and triglyceride levels <300 mg/dl. The patients were randomly assigned to either receive pravastatin (10 mg/daily, n=176) or not (n=177). The primary endpoint was a composite of death, nonfatal myocardial infarction (MI), unstable angina (UA), stroke, revascularization, and rehospitalization because of other cardiovascular disease. The follow-up period was 9 months. The primary endpoint occurred in 31 patients (17.9%) in the pravastatin group and 55 patients (31.4%) in the non-pravastatin group (relative risk, 0.56; 95% confidence interval, 0.36–0.87). There were no significant differences in the risk of death, nonfatal MI, UA, and stroke between the 2 groups, although the pravastatin group had a lower risk of need for revascularization.

Conclusion For patients with AMI, early and low-dose pravastatin therapy (10 mg/daily) reduces recurrent major adverse cardiac events, mostly the requirement for revascularization. (Circ J 2008; 72: 17–22)

Key Words: Myocardial infarction; Prevention; Statins

Recent clinical studies have revealed the efficacy of lipid-lowering therapy, particularly with statins, in the primary1,2 and secondary3–5 prevention of cardiac events in patients with coronary artery disease. Several studies have revealed that early statin therapy is associated with improved hospital outcomes6,7 and that aggressive lipid lowering is associated with better outcomes8 in patients with acute coronary syndromes (ACS). However, recent trials failed to show conclusive benefit of early statin therapy in patients with ACS9,10. Furthermore, despite the recommendation of evidence-based statin dose in patients with ACS, the majority of Japanese patients with ACS are administered low-dose statins.

Accordingly, we designed and conducted a randomized trial, the Osaka Acute Coronary Insufficiency Study (OACIS)-LIPID study, to investigate whether early reduction in total cholesterol (TC) with low-dose pravastatin will improve the mid-term prognosis of patients with acute myocardial infarction (AMI).

Methods

Study Population Patients are enrolled from the OACIS registry. The OACIS is a prospective, multicenter observational study, in which 25 collaborating hospitals in Japan are recording demographic, procedural, and outcome data, and collecting blood samples from patients with AMI. The registry is designed to collect uniform, prospective data on patients with AMI that can be used to assess clinical variables, therapeutic procedures, and clinical events11,12 and to collect DNA samples from patients with AMI that can be used to investigate whether common genetic variations are involved in the pathogenesis of AMI13,14. The diagnosis of AMI required the presence of 2 of the following 3 criteria: (1) clinical history of central chest pressure, pain, or tightness lasting for 30 min or more, (2) typical electrocardiographic changes...
(ie, ST-segment elevation >0.1 mV in at least 1 standard or 2 precordial leads, ST-segment depression >0.1 mV in at least 2 leads, abnormal Q wave, or T wave inversion in at least 2 leads), and (3) an increase in the serum creatine kinase activity more than twice the normal laboratory value. All patients presenting within 1 week after the onset of AMI were registered prospectively, as soon as the diagnosis of AMI had been made. Between May 2000 and December 2003, 2,560 patients with AMI were screened, and finally 353 patients were enrolled in the OACIS-LIPID study at 14 hospitals in Japan (see Appendix 1). The AMI patients are included in the study if the serum level of TC was between 200 and 250 mg/dl and that of triglycerides did not exceed 300 mg/dl. Patients were excluded if they were receiving concurrent therapy with any statins or had a history of side-effects associated with any statin. Other exclusion criteria were: evidence of life-threatening arrhythmia, severe chronic congestive heart failure (New York Heart Association class III–IV), hepatic dysfunction, renal failure, cerebrovascular disease, poorly controlled diabetes, pregnancy, lactation, age <20 years, and unable to take medication or absence of written informed consent. Patients whom the doctors consider inappropriate for any other reason were also not included.

**Study Design**

The trial was designed as a prospective, randomized, open-labeled, blinded-endpoint evaluation, multicenter study to test the hypothesis that early use of pravastatin (10 mg/daily) will improve the mid-term prognosis of patients with AMI and mild to moderate hyperlipidemia. Details of the study design have been reported previously. The protocol was approved by the relevant institutional ethics committees, and written informed consent was given by all patients. Eligible patients were randomized to 1 of 2 treatment groups in the week after onset of AMI. One group was assigned pravastatin, and the other was not. All patients received instructions and counseling to promote compliance with the National Cholesterol Education Program Step I diet. We set the initial dose of pravastatin at 10 mg/day, as recommended by the Ministry of Health, Labour and Welfare of Japan. Physicians were allowed to change the dose of pravastatin for the pravastatin group and use lipid-lowering drugs other than statins for the non-pravastatin group. Both groups received dietary counseling. Patients were seen in follow-up at 3, 6, and 9 months after the initiation of therapy. Participating hospitals were encouraged to perform repeat catheterization before the end of the study and were also encouraged to perform revascularization when ischemic symptoms or signs were clearly observed. Laboratory testing was performed at baseline and at 9 months. All hospitals were encouraged to enter consecutive eligible patients with AMI, irrespective of treatment strategy or outcome.

---

**Fig 1. Trial profile.**
Endpoints
The outcome measures (endpoints) were a combination of death, non-fatal myocardial infarction (MI), unstable angina (UA), revascularization and non-fatal stroke, and re-hospitalization because of other cardiovascular diseases. The endpoints were strictly evaluated by the Endpoint Classification Committee of the OACIS study. Principal investigators were not informed about which group the patient belonged to when they classified the endpoint of the patient.

Statistical Analysis
The expected occurrence of an endpoint in patients with non-pravastatin was 35%, based on data from the OACIS. To detect a 50% reduction in this occurrence rate in the pravastatin-treated group using a log rank test with a 2-sided significance level of 5% and power of 95%, a sample size of 160 patients per each group was required. Considering the number of patients who were excluded, we set the number at 175 patients for each group. All efficacy analyses were based on the intention-to-treat basis. Continuous variables between groups were compared by t-test. Categorical variables were compared by the chi-square test. The primary combined endpoint was analyzed by time of first event, using a Cox proportional hazards model. Cumulative event curves were plotted by the Kaplan-Meier method and the difference was tested by log-rank test. The occurrence of each endpoint was analyzed using the chi-square test. In the case of low cell count, the Fisher exact test was used instead of the chi-square test. Analyses of data were performed using statistical software (SPSS version 11.0; SPSS Japan Inc, Tokyo, Japan). For all analyses, significance was defined as \( p<0.05 \).

Results
Patient Enrollment and Characteristics
Of the 2,560 patients screened, 353 patients were enrolled; 176 were randomly assigned to receive pravastatin and 177 were randomly assigned to receive standard AMI therapy without pravastatin (Fig 1). The demographic and clinical characteristics of the patients assigned to the 2 treatment groups were similar at baseline (Table 1). Treatment with guideline-recommended therapies, such as angiotensin-converting enzyme inhibitors, \( \beta \)-blockers, and antiplatelet agents, was similar between the 2 treatment groups (Table 1). Eighty-six percent of patients underwent percutaneous coronary intervention (PCI) for the treatment of their AMI. The mean time from symptom onset to beginning the randomized treatment was 8.7±6.5 days (range 1–28). The mean follow-up was 259 days: 3 patients in the pravastatin group and 2 in the non-pravastatin group discontinued follow-up.

Serum Lipid Levels
At baseline, there were no differences between the 2 treatment groups (Table 1). After 9 months, treatment with pravastatin lowered the low-density lipoprotein (LDL)-cholesterol levels by 22% from 150 mg/dl to 117 mg/dl (pc
During the 9-month study period, the primary endpoint occurred in 31 patients (17.9%) in the pravastatin group and in 51 patients (31.4%) in the non-pravastatin group (Table 2). Pravastatin treatment significantly reduced the risk of the primary combined endpoint (hazard ratio 0.56; 95% confidence interval 0.36–0.87; p=0.006). Fig 2 shows the Kaplan-Meier curves for all primary endpoints. There were no significant differences in the risk of death, non-fatal MI, UA or non-fatal stroke between the pravastatin group and non-pravastatin group, although the pravastatin group had a lower risk of revascularization, especially PCI (12.7% vs 20.6%, p=0.049).

**Discussion**

In this trial, early treatment with pravastatin (10 mg/daily) reduced the recurrent major adverse cardiac events in patients with AMI. There was a 44% relative reduction in the primary combined endpoint of death, nonfatal MI, UA, stroke, revascularization, and other cardiovascular diseases. Randomized controlled trials have demonstrated that treatment with statins initiated 3–6 months after ACS reduces long-term mortality and recent studies indicate that statins have favorable physiologic effects within weeks. In conjunction with their lipid-lowering effect, statins have been shown to improve endothelial function, reduce platelet aggregability and thrombus formation, and reduce vascular inflammation effects that would be expected to have a favorable impact in the early period following ACS. Until recently, information regarding the timing of the initiation of statin therapy following ACS had been limited to observational studies and although recent trials have evaluated early initiation of statins after ACS, the results were inconsistent. The Myocardial Ischemia with Aggressive Cholesterol Lowering (MIRACL) trial and the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial showed that early statin treatment reduces the risk of adverse cardiac events after ACS. However, the Fluvastatin on Risk Diminishment after Acute Myocardial Infarction (FLORIDA) trial, the Pravastatin in Acute Coronary Treatment (PACT) trial, and the A to Z trial failed to show an effect of early statin treatment on adverse cardiac events. Differences among these trials with regard to disease stabilization may have contributed to differences in early outcomes. In the MIRACL trial eligible patients were randomly assigned to treatment with atorvastatin or placebo between 24 and 96h after hospital admission and patients were excluded if coronary revascularization was planned or anticipated at the time of screening. In the PROVE IT-TIMI 22 trial, patients were eligible for inclusion if they had been hospitalized for an ACS in the preceding 10 days and patients had to be in a stable condition and were enrolled after PCI if one was planned. It seems that the MIRACL and PROVE IT-TIMI 22 trials enrolled patients after their condition had stabilized, whereas the FLORIDA and PACT trials commenced within 24h of onset. In the A to Z trial, patients were entered only if they presented with ST-elevation ACS, were stabilized for at least 12 consecutive hours within 5 days of onset, and met at least 1 high-risk factor. The FLORIDA, PACT, and A to Z trials seems to include more unstabilized or higher risk patients than the MIRACL and PROVE IT-TIMI 22 trials. In unstable or high-risk patients, factors that are unlikely to be affected by cholesterol lowering, such as left ventricular dysfunction, ventricular arrhythmias, and mechanical complications represent the major determinants.

### Table 2 Cardiovascular Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Pravastatin (n=176)</th>
<th>Non-pravastatin (n=177)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined endpoints, %</td>
<td>17.9</td>
<td>31.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Death, %</td>
<td>1.7</td>
<td>1.1</td>
<td>0.643*</td>
</tr>
<tr>
<td>Non-fatal MI, %</td>
<td>0.6</td>
<td>1.7</td>
<td>0.622*</td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>2.9</td>
<td>2.9</td>
<td>0.985</td>
</tr>
<tr>
<td>Revascularization, %</td>
<td>12.7</td>
<td>20.6</td>
<td>0.049</td>
</tr>
<tr>
<td>PCI, %</td>
<td>11.0</td>
<td>18.3</td>
<td>0.054</td>
</tr>
<tr>
<td>CAGB, %</td>
<td>1.7</td>
<td>2.3</td>
<td>0.506*</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>0.0</td>
<td>1.1</td>
<td>0.252*</td>
</tr>
<tr>
<td>Rehospitalization because of other cardiovascular diseases, %</td>
<td>0.0</td>
<td>4.0</td>
<td>0.008</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.0</td>
<td>2.8</td>
<td>0.061*</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>0.0</td>
<td>0.6</td>
<td>0.503*</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0.0</td>
<td>0.6</td>
<td>0.503*</td>
</tr>
</tbody>
</table>

*Fisher’s exact test.

Abbreviations see in Table 1.
of outcome. These features in the FLORIDA, PACT, and A to Z trials may have resulted in relatively less response to statin therapy. In the OACIS-LIPID trial, the mean time from symptom onset to starting randomized treatment was 8.7 days and patients were excluded if they had evidence of life-threatening arrhythmia, severe chronic congestive heart failure, hepatic dysfunction, renal failure, cerebrovascular disease, or poorly controlled diabetes. Therefore, we think that the OACIS-LIPID trial entered relatively stable or low-risk patients, as did the MIRACL and PROVE IT-TIMI 22 trials, and hence showed positive results.

The effect on events manifested shortly after discharge from hospital and persisted throughout the study, as demonstrated in Fig 2 in which the curves continue to diverge. We need to pay careful attention to the fact that the majority of patients underwent revascularization by PCI. Similar clinical effects were previously reported using pravastatin treatment. Early restoration of endothelial function by HMG-CoA reductase inhibitors and associated reduction of transient myocardial ischemia may have resulted in less interventions. Furthermore, a recently published meta-analysis suggests that the clinical benefit of statins vs placebo is proportional to treatment changes in LDL, and it is possible that LDL lowering may be more closely related to long-term than to short-term outcomes.

An interesting point is that, despite the smaller dose of pravastatin administered in this trial, there was an equivalent reduction in the risk of coronary events to the value seen in previous studies. Possible reasons include chance, synergistic effects of Japanese-style diet therapy, or high-sensitivity of Japanese to pravastatin. Recent data from primary (and secondary) prevention trials done in Japan suggest the efficacy of low-dose statins.

The statistical difference of the effect on events was significant; however, careful attention should be paid because for the most part the events were revascularizations. Because the decision to perform a coronary intervention is partially based on subjective factors, we were not able to exclude the existence of potential biases. Although further studies are needed to uniform the beneficial effect of pravastatin achieved with a rather small reduction in lipids, early treatment with low-dose pravastatin significantly reduced recurrent major adverse cardiac events in Japanese patients with AMI in the OACIS-LIPID trial.

Acknowledgments

We thank Kuniko Miyoshi, Chizuru Hanauguchi, Hiroko Machida, Mariko Yoneeda, Kana Sakatani, Nagisa Yoshikoa, Miki Shinkura, Tomomi Miyai, Saeko Kikimoto, Tomoko Inoue, and Aki Yabuuchi for their excellent assistance with data collection. This work was supported by a Grant-in-Aid for Scientific Research (C) (21) (#15590743 and #17590730) from the Japan Society for the Promotion of Science, Tokyo, Japan and by research funds from the Japan Arteriosclerosis Prevention Fund, Tokyo, Japan.

References

Relation of C-reactive protein and one-year survival after acute myocardial infarction with versus without statin therapy. Am J Cardiol 2005; 96: 617–621.


Appendix 1

The following institutions and persons participated in the OACIS-LIPID trial.

Sakurabashi Watanabe Hospital, Osaka: Fujii K, Ito H; Osaka Police Hospital, Osaka: Kodama K, Hirayama A; Kansai Rosai Hospital, Amagasaki: Nagata S, Nanto S, Morozumi T; Osaka General Medical Center, Osaka: Fukunumi M, Shimomata T; Osaka Rosai Hospital, Sakai: Yamada Y, Tanouchi J, Nishino M; Kawachi General Hospital, Higashi-Osaka: Mishima M, Lim YJ; Higashi-Osaka City General Hospital, Higashi-Osaka: Kijima Y; Osaka National Hospital, Osaka: Kusukuka H, Koretsune Y, Yasumura Y; Osaka Minami National Hospital, Kawachinagano: Kinoshita N, Imai K; Osaka Kosei Nenkin Hospital, Osaka: Sasaki T; Osaka Railway Hospital of West Japan Railway Company, Osaka: Ezumi A; Kaizuka City Hospital, Kaizuka: Morita H, Lee JM; Teramoto Memorial Hospital, Kawachinagano: Hishida E; Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, Suita: Otsu K, Yamamoto K; Department of Medical Information Science, Osaka University Graduate School of Medicine, Suita: Takeda H, Matsumura Y.