The Impact of Pravastatin Pre-Treatment on Periprocedural Microcirculatory Damage in Patients Undergoing Percutaneous Coronary Intervention

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Objectives  This study evaluated the effect of pravastatin pre-treatment on post-procedural index of microcirculatory resistance (IMR) values that are introduced for assessing the status of the microcirculation independently of the epicardial area.

Background  Pre-treatment with statins decreased the incidence of cardiac enzyme increase after percutaneous coronary intervention (PCI). However, 2 different etiologies, distal embolization of atheroma or ischemia caused by side-branch occlusion, cannot be differentiated by measuring cardiac enzyme levels.

Methods  Eighty patients with stable angina were randomly assigned to either pravastatin treatment (20 mg/day, n = 40) or no treatment (n = 40) 4 weeks before elective PCI. An intracoronary pressure/temperature sensor-tipped guidewire was used. Thermodilution curves were obtained during maximal hyperemia. The IMR was calculated from the ratio of the mean distal coronary pressure at maximal hyperemia to the inverse of mean hyperemic transit time. Creatine kinase-myocardial band and troponin I values were measured at baseline and at 8 and 24 h after PCI.

Results  Post-PCI troponin I levels tended to be lower in patients with pravastatin treatment (median: 0.13 [interquartile range (IQR): 0.10 to 0.31] vs. 0.22 [IQR: 0.10 to 0.74] ng/ml, p = 0.1). However, patients with pravastatin treatment had significantly lower IMR than did patients without pravastatin treatment (median: 12.6 [IQR: 8.8 to 18.0] vs. 17.6 [IQR: 9.7 to 33.9], p = 0.007). Multivariate analysis revealed that the lack of pravastatin pre-treatment was the only independent predictor of post-PCI impaired IMR (p = 0.03).

Conclusions  Post-PCI measurement of the IMR confirmed that pre-treatment with pravastatin was associated with reduced microvascular dysfunction induced by PCI regardless of side branch occlusions. These data suggest that pre-treatment with statin is desired in patients undergoing elective PCI. (The Impact of Pravastatin Pretreatment on Periprocedural Microcirculatory Damage After Percutaneous Coronary Intervention; UMIN000002885) (J Am Coll Cardiol Intv 2011;4:513–20) © 2011 by the American College of Cardiology Foundation
The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are widely used to decrease cholesterol synthesis and are well established to reduce vascular diseases (1–3). As statins became more widely used in greater numbers of patients, their effects beyond lipid lowering began to emerge. Such pleiotropic effects include improvement of endothelial dysfunction (4), increased nitric oxide bioavailability, antioxidant effects, anti-inflammatory properties, and stabilization of atherosclerotic plaques. Several randomized studies demonstrated that pre-treatment with statins reduced the incidence of myocardial infarction after percutaneous coronary intervention (PCI) in patients with stable angina pectoris (5,6).

Myocardial necrosis, assessed by cardiac marker elevation, is relatively frequent after elective PCI, occurring in 10% to 50% of cases (4,7,8). Previous studies have reported that patients with cardiac marker increase after PCI had higher late mortality and more unfavorable event-free survival than did those patients without cardiac marker increase (9,10).

Abbreviations and Acronyms

CK-MB = creatine kinase-myocardial band
FFR = fractional flow reserve
IMR = index of microcirculatory resistance
IQR = interquartile range
IVUS = intravascular ultrasound
LDL = low-density lipoprotein
PCI = percutaneous coronary intervention

IMR has been validated in an animal model and tested in stable angina patients (13–15). The advantages of IMR over current methods for assessing the microvascular function are its relative ease of performance and interpretation, its independence of the epicardial vessel stenosis, its reproducibility, and its quantitative nature. We conducted a prospective and randomized study to evaluate the effect of pravastatin pre-treatment on post-procedural microvascular impairment assessed by post-PCI IMR values and cardiac marker in elective PCI for patients with stable angina pectoris.

Methods

Study population and study protocol. This was a randomized nonblind, prospective study performed in a single center. Inclusion criteria were the presence of typical stable effort angina or a positive stress test, and an indication for PCI of a single de novo lesion >50% diameter stenosis in a native coronary artery. Exclusion criteria were left ventricular ejection fraction <30%, acute coronary syndrome in the previous month, a history of myocardial infarction in the target vessel–related territory, a history of coronary artery bypass grafts, any increase in creatine kinase-myocardial band (CK-MB) or troponin I above the upper normal limit at the time of randomization, renal dysfunction with creatinine >3 mg/dl, chronic total occlusion, in-stent restenosis, left main lesion, contraindications to adenosine, and previous treatment with statins.

Between April 2007 and March 2009, 414 patients underwent elective PCI for stable angina pectoris. Of those, 166 patients were excluded because of previous or current treatment with statins; 82 because of in-stent restenosis lesion; 32 because of a potential difficulty to cross the pressure wire to the lesion due to small diffusely diseased, tortuous, occluded, or calcified vessels; 24 because of renal dysfunction; 21 because of low ejection fraction; 5 because of previous bypass surgery; and 4 because of previous myocardial infarction in the target vessel–related territory. Thus, 80 patients fulfilling the inclusion criteria were scheduled for elective PCI and were included in the study. Patients were randomly assigned to pravastatin treatment (20 mg/day, which is the maximum approved dose in Japan where the study was performed) starting 30 days before the planned PCI (pravastatin group) or to no statin treatment (control group); 40 patients were assigned to the pravastatin group and 40 patients to the control group. Patients were randomized independently of their lipid levels. According to our standard protocol, all patients without contraindications were pretreated with aspirin (100 mg/day) and ticlopidine 200 mg twice a day or clopidogrel 75 mg/day at least 7 days before the procedure. Before intervention, all patients received 100 international units/kg intravenous bolus of unfractionated heparin. Additional heparin boluses were given to maintain activated clotting time >300 s. All patients provided written informed consent, and approval of the presiding ethical committee was obtained.

Coronary physiological measurements and intervention. PCI was performed in a usual manner using coronary stents. All coronary physiological assessments and interventions were performed after intracoronary administration of 0.5 mg isosorbide dinitrate. The fractional flow reserve (FFR) was measured in each patient before and after PCI, and IMR was measured after PCI using previously described principles and methods (13–15). Briefly, an intracoronary pressure/temperature sensor-tipped wire (Radi PressureWire Certus, St. Jude Medical, Minneapolis, Minnesota) was advanced through a 6-F guiding catheter to position the pressure sensor at a point 5 to 10 mm distal from the distal edge of the stent. Intravenous adenosine triphosphate (140 μg/kg/min) was administered to induce steady-state maximal hyperemia. Then, 3 injections of saline (3 ml at room temperature) were administered to the coronary artery through the guiding
catheter at maximal hyperemia. The hyperemic transit time was measured as the time that elapsed between when one-half of the saline had been injected (defined as T0, and determined on the temperature curve from the shaft of the wire) and when one-half of the saline had passed the sensor. Simultaneous measurements of mean distal coronary pressure were also made in the maximal hyperemic states. FFR was measured by dividing the mean distal coronary pressure by the mean aortic pressure during maximal hyperemia (16,17). IMR was calculated as mean distal coronary pressure multiplied by the hyperemic mean transit time.

**Angiographic analysis.** Cineangiograms were analyzed using a computer-assisted, automated edge-detection algorithm (CMS; Medis Medical Imaging Systems, Raleigh, North Carolina) by an independent observer who was unaware of the intravascular ultrasound (IVUS) and physiological measurements using standard qualitative and quantitative definitions and measurements. The occurrence of angiographic complications during PCI was recorded. Angiographic complications included major side branch occlusions, abrupt intraprocedural vessel closure, major arterial dissection, thrombus formation, and prolonged slow-no reflow.

**IVUS imaging and analysis.** IVUS examinations were attempted for all patients before and after PCI after intracoronary administration of 0.5 mg isosorbide dinitrate using a commercially available system (Atlantis Pro, Boston Scientific, Natick, Massachusetts). The 40-MHz IVUS catheter was advanced >10 mm beyond the lesion and an imaging run (using automated transducer pullback at 0.5 mm/s) was performed to a point >10 mm proximal to the lesion. Lesion plaque composition was assessed visually at the minimum lumen cross-sectional area site. Image slices with the minimum lumen area and the proximal and distal references were identified and measured. Using planimetry software (Tape Measure, INDECT Systems, Santa Clara, California), vessel area and lumen area were measured. Plaque area (vessel minus lumen area), plaque burden (plaque area divided by vessel area), and remodeling index (lesion vessel area divided by mean reference vessel area) were calculated.

**Assessment of cardiac markers.** The CK-MB and troponin I levels were systematically measured before intervention, at 6 to 8 h after the procedure, and at 18 to 24 h after the procedure. If cardiac marker levels were elevated, serial measurements were performed every 6 to 8 h until they returned to baseline. All cardiac marker determinations were performed in the clinical chemistry laboratory by the mass-determination methods (normal range 0 to 16 units/l for CK-MB and 0 to 0.1 ng/ml for troponin I).

**Statistics.** Continuous variables were reported as mean ± SD or median (interquartile ranges). The unpaired Student t test was used to test the differences between 2 sets of data with normal distributions. If normality tests failed, the Mann–Whitney U test was used. Relationships between studied variables were assessed by linear regression. Categorical variables were assessed by chi-square statistics. Intraobserver variability in IMR measurements was assessed by calculation of the Pearson correlation coefficients. Multivariate logistic regression analysis was performed to determine independent predictors of impaired IMR after PCI. Univariate analyses were first conducted to identify potential factors for impaired IMR. The likelihood-ratio test was used, and the variables with a p value <0.2 were included in the multivariate model. A p value <0.05 was considered statistically significant.

**Results**

**Baseline clinical characteristics.** Baseline clinical and procedural variables in the pravastatin and control groups are shown in Tables 1, 2, and 3, respectively. The 2 groups were similar with regard to age, sex, cardiovascular risk factors, left ventricular function, and concomitant medical therapies at the time of randomization. Coronary anatomy, lesion type, procedural characteristics, use of drug-eluting stents, and diameter and length of stents were also similar. Procedural success was achieved in all patients of the 2 groups. There were no in-hospital complications (death or need for emergent revascularization). Total cholesterol and low-density lipoprotein cholesterol levels at the time of PCI were significantly lower in the pravastatin group than in the control group. There was no incidence of significant increase in serum liver enzymes and/or myopathy in the pravastatin group.

**Table 1. Baseline Clinical Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n = 40)</th>
<th>Control (n = 40)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>68 ± 8</td>
<td>68 ± 11</td>
<td>0.8</td>
</tr>
<tr>
<td>Male</td>
<td>32 (80)</td>
<td>32 (80)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (70)</td>
<td>22 (55)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (45)</td>
<td>17 (43)</td>
<td>0.8</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11 (28)</td>
<td>14 (35)</td>
<td>0.5</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>12 (30)</td>
<td>9 (23)</td>
<td>0.4</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>5 (13)</td>
<td>4 (10)</td>
<td>0.7</td>
</tr>
<tr>
<td>Previous coronary intervention</td>
<td>16 (40)</td>
<td>8 (20)</td>
<td>0.1</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>60 ± 9</td>
<td>63 ± 7</td>
<td>0.2</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>24 (60)</td>
<td>16 (40)</td>
<td>0.1</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>7 (18)</td>
<td>3 (8)</td>
<td>0.2</td>
</tr>
<tr>
<td>AT II antagonist</td>
<td>19 (48)</td>
<td>25 (63)</td>
<td>0.2</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>13 (33)</td>
<td>16 (40)</td>
<td>0.5</td>
</tr>
<tr>
<td>Nitrates</td>
<td>4 (10)</td>
<td>7 (18)</td>
<td>0.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24 ± 3</td>
<td>24 ± 2</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration of pravastatin treatment, days</td>
<td>35 ± 12</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; AT II = angiotensin II; CAD = coronary artery disease.
Procedural, angiographic, and IVUS analysis. Procedural characteristics, angiographic and IVUS data, and pre-PCI FFR values were comparable in both groups (Table 4). Glycoprotein IIb/IIIa inhibitors were not used because they are not approved in Japan. The incidence of angiographic complications during the procedure was similar between the 2 groups. The frequency of major side branch occlusions was 5% in the pravastatin group and 8% in the control group (p = 0.9). Major arterial dissection occurred in only 1 patient, who was in the pravastatin group.

Physiological measurements and cardiac markers. After PCI, physiological parameters were successfully obtained in all patients. Although FFR values were similar between the 2 groups, IMR values were significantly lower in the pravastatin group than in the control group (median: 12.6 [interquartile range (IQR): 8.8 to 18.0] vs. 17.6 [IQR: 9.7 to 33.9], p = 0.007). There was no correlation between IMR and FFR (r = 0.05, p = 0.7). For IMR measurements, the correlation coefficient was 0.908 (mean difference: 6.1 ± 7.4).

An increase of CK-MB above the upper normal limit occurs in 23% of patients in the pravastatin group versus 33% in the control group (p = 0.3). Post-PCI elevations of troponin I above the upper normal limit occurred in 58% of patients in the pravastatin group versus 60% in the control group (p = 0.8). However, troponin I elevation more than 5× the upper limit of normal level tended to be less common in the pravastatin group than in the control group (13% vs. 33%, p = 0.06). Although post-PCI CK-MB and troponin I values were significantly greater in patients with side branch occlusion than in those without side branch occlusion (median: 17.0 [IQR: 16.8 to 33.8] vs. 11.0 [IQR: 9.0 to 15.0], p = 0.03; 0.36 [IQR: 0.25 to 2.56] vs. 0.13 [IQR: 0.10 to 0.37], p = 0.01), post-PCI IMR values were similar between them (median: 10.7 [IQR: 8.2 to 14.5] vs. 14.3 [IQR: 9.4 to 26.5], p = 0.3). In patients with side branch occlusion, post-PCI cardiac markers were similar between patients in the pravastatin and control groups.
Mean post-PCI IMR values were significantly greater in patients with troponin I elevation more than 5× the upper limit of normal level (n = 18) than in patients without troponin I elevation more than 5× the upper limit of normal level (n = 62): 31.5 (IQR: 17.0 to 54.1) and 11.6 (IQR: 9.0 to 18.0), respectively (p < 0.001). Distribution pattern of IMR values both in the pravastatin group and the control group according to post-PCI troponin I value was shown in Figure 1. Some patients indicated low post-PCI IMR value with troponin release (Fig. 2). In the whole sample, we found a weak positive correlation between IMR and pre-PCI C-reactive protein levels (r = 0.28, p = 0.01).

**Predictors of microcirculation damage after PCI.** As a point of reference, in a study including patients with stable coronary disease and no obvious microvascular dysfunction, the mean IMR was 22 (14). There were 7 patients (18%) with IMR >22 in the pravastatin group and 16 (40%) in the control group (p = 0.03). Multivariate logistic regression analysis was performed to determine the independent predictors of microcirculation damage after PCI. The following variables were tested (all with p < 0.2 in univariate analysis): pravastatin, stent size, maximum balloon inflation pressure, diabetes mellitus, C-reactive protein level, IVUS plaque burden, and creatinine level. The only independent predictor of IMR >22 was absence of pravastatin before PCI (p = 0.03).

**Discussion**

The main finding of this study is that pravastatin therapy before PCI is associated with preserved coronary artery physiology after PCI at the level of the microvascular bed assessed with IMR, an invasive wire-based quantitative measure of microvascular function. Our data suggest that pre-treatment with statin is desired in patients undergoing elective PCI for stable angina pectoris.

Asymptomatic myocardial damage, evaluated by post-procedural cardiac markers elevation, has been shown to occur frequently after otherwise successful PCI (4–8). It has been reported that patients with cardiac marker increases had higher late mortality and more unfavorable event-free survival than did those patients with a normal cardiac marker after PCI (9,10). It is generally considered that the mechanism of cardiac marker release is distal embolization of atherothrombotic material accompanying the plaque disruption that is essential to the success of the PCI procedure. Previous studies reported that thrombosis either of a side branch occlusion or by distal embolization appears to be a major culprit for cardiac marker release after PCI (18–20). However, these different etiologies of cardiac marker release after PCI cannot be differentiated by measuring serum cardiac marker levels. The IMR has been used in humans to assess the microcirculation in various clinical settings, such as in acute myocardial infarction, (21), stable angina pectoris (16), and after cardiac transplantation (22).

In this study, the IMR was measured after coronary stenting. Therefore, there was no angiographically residual significant stenosis present, which allowed the use of the simpler equation for IMR. In this study, patients with pravastatin treatment had significantly lower IMR value than did patients without pravastatin treatment. Although the exact mechanism is unclear, these observations suggest that pre-treatment with pravastatin induces important changes in the plaque morphology, reducing inflammatory activity and favoring a reduction in the relative content of cholesterol esters that are important factors influencing plaque stability. Our results support the hypothesis that statins stabilize atherosclerotic plaques and reduce distal embolization of plaque materials.

In several randomized trials (1–3), statin therapy was generally started after PCI; in addition, those trials were not specifically focused on the effect of statins on periprocedural microvascular damage. In the current study, patients were started on pravastatin treatment 1 month before PCI regardless of their cholesterol levels. A previous randomized study (5) indicated that pre-treatment with atorvastatin 40 mg/day for 7 days reduced serum cardiac marker elevation after PCI. Pravastatin was used in the current study, because some studies reported that the lipophilic statins would be expected to penetrate cell membranes more effectively than the more hydrophilic statins, causing more side effects (23). In line with the current study, a previous study (24) demonstrated that 2 weeks of treatment with pravastatin improved vascular abnormality through alteration in microcirculation without any episode of side effects. The correlation between the reduction of low-density lipoprotein (LDL) cholesterol and the post-PCI IMR value was not significant in the current study (data were not shown). One of the reasons might be that patients

![Figure 1. Distribution of IMR Values Among Patients Treated With and Without Pravastatin According to Post-PCI Troponin I Value](image)

**Solid circles** show troponin I >5× the upper limit of normal level; **open circles** show troponin I <5× the upper limit of normal level. IMR = index of microcirculatory resistance; PCI = percutaneous coronary intervention.
were started on pravastatin treatment 1 month before PCI in the current study. The mechanisms underlying the beneficial effects of pravastatin in reducing microvascular damage after PCI are not completely clear. Pleiotropic effects unrelated to LDL cholesterol reduction might be one of the mechanisms underlying the prevention of microvascular damage during PCI. Animal studies of cholesterol reduction demonstrate changes in plaque structure including reduction of macrophage numbers and matrix metalloproteinase-1 expression and increases in interstitial collagen content resulting in increased plaque stability (25). Clinical studies of statin treatment, using IVUS, have consistently demonstrated increases in hyperechogenicity index (suggesting an increase in fibrous tissue), reductions in the plaque lipid pool, but only modest reductions in plaque volume (26). Another potential mechanism may be through the anti-inflammatory properties of pravastatin. Chan et al. (27) reported that the anti-inflammatory effects of statins plays a role, showing that the benefit was higher in patients with high C-reactive protein. This anti-inflammatory effect of statins might contribute to reduce microcirculation damage due to microembolization during PCI. In the current study, there was a linear relationship between post-PCI IMR values and pre-PCI C-reactive protein levels.

The results of the current study support the previous reports demonstrated that statin therapy is an independent predictor of survival benefit after PCI (28). The advantage of statins in coronary heart disease can be explained not only by their lipid-lowering effect, but also by nonlipid-related mechanism, the “pleiotropic effects.” The pleiotropic effects of statins are believed to include antiproliferative, anti-inflammatory, and immunomodulatory actions; the property to improve endothelial dysfunction; and increasing of nitric oxide bioavailability.

**Study limitations.** This study was a single-center study with a relatively small study population. Further multicenter studies are required to reconfirm the results in a larger number of patients. Even though all patients were randomly assigned to either pravastatin treatment or no treatment, a placebo group was not included in this study. In the current study...
study, the 20-mg dose of pravastatin was used, because it is the maximal approved dose in Japan. The 20-mg dose of pravastatin seems to be less than the dose (40-mg dose of atorvastatin) in trials in Western countries (5). Therefore, our results may not be applicable to other ethnic groups, but the degree of LDL cholesterol reduction (−31%) by 20-mg dose of pravastatin in this study was larger than that with 40-mg dose in the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial (−22%). Quantitative assessment of the plaque composition with radio frequency analysis of ultrasound backscatter signals was not performed in the current study. The baseline IMR values were not calculated, because coronary wedge pressure before PCI was not measured in this study. The duration of these microcirculatory damages is unknown; in fact, in the absence of cardiac marker elevation, there may not be any damage. The statistical power was insufficient to find the correlation between the reduction of LDL cholesterol level and prevention of microvascular damage during PCI. Finally, it is still unknown whether impaired IMR can predict long-term outcomes in patients with stable angina pectoris. Further investigation is needed to clarify the association between post-procedure IMR impairment and adverse short- and long-term clinical outcomes.

Conclusions

Post-PCI measurement of the IMR confirmed that pre-treatment with pravastatin was associated with reduced microvascular dysfunction induced by PCI regardless of side branch occlusions. These data suggest that pre-treatment with statins is desired in patients undergoing elective PCI for stable angina pectoris.

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