Local Delivery of Argatroban for the Prevention of Restenosis After Coronary Balloon Angioplasty

— A Prospective Randomized Pilot Study —

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for the 3D-CAT investigators

**Background**

Effective pharmacological prevention of restenosis using the systemic administration of various drugs that were effective for the prevention of restenosis in experimental studies has not been reported. The purpose of this study was to evaluate whether the local delivery of a potent thrombin inhibitor, argatroban, using a local drug delivery device would prevent restenosis after plain old balloon angioplasty (POBA).

**Methods and Results**

Seventy patients with chronic coronary artery disease requiring POBA were randomly assigned to either the control group (n=35) or the argatroban group (n=35). In the argatroban group, argatroban was administered intravenously for 30 min before the POBA and intracoronarily into the dilated site using a Dispatch™ catheter immediately after the POBA, followed by a postoperative intravenous infusion for 4 h. The angiographical lesion restenosis and clinical restenosis rates at follow-up were significantly lower in the argatroban group (27% and 14%) than in the control group (56% and 37%; p=0.02 and p=0.03, respectively). There was no major complication during the procedure.

**Conclusion**

The local delivery of argatroban is safe and effective in preventing restenosis after balloon angioplasty. (Circ J 2004; 68: 615–622)

**Key Words:** Coronary angioplasty; Direct thrombin inhibitor; Local drug delivery; Restenosis

The clinical efficacy of coronary balloon angioplasty (plain old balloon angioplasty: POBA) is limited by restenosis, which occurs in 30–50% of cases despite a successful procedure.1–4 However, in previous clinical trials5–9 there has not been effective pharmacological prevention of restenosis using the systemic administration of various drugs that were found to be effective for the prevention of restenosis in experimental studies. One of the major factors in the failure of restenosis prevention in these clinical trials could be that the systemic administration of drugs resulted in a concentration at the site of a balloon injury that was too low. Accordingly, it has been anticipated that the local delivery of a drug at high concentration may reduce the restenosis rate after POBA. However, the pharmacological prevention of restenosis using a local drug delivery system has not yet been tested in clinical trials except for one small-scale trial.10

It was recently reported that the messenger RNA (mRNA) of a thrombin receptor is expressed in medial smooth muscle cells in the very early phase after a balloon catheter injury (within 6 h).11,12 Moreover, pre-treatment with hirudin (a direct thrombin inhibitor) was found to reduce vascular lesion development after balloon injury in experimental studies.13,14 Thus, it is thought that restenosis may be prevented or minimized by the local administration of a direct thrombin inhibitor. Argatroban is a direct thrombin inhibitor that has a more potent inhibitory effect on fibrin- or clot-incorporated thrombin than other thrombin inhibitors such as heparin and hirudin.15,16 Tomaru et al reported that the local delivery of argatroban using a double-balloon catheter reduced intimal thickening after balloon injury in an experimental study.17 Accordingly, we conducted a prospective, randomized, controlled clinical trial to assess the effect of the local delivery of argatroban as a direct thrombin inhibitor using a Dispatch™ catheter system18 (SIMED Life Systems, Inc, Maple Grove, MN, USA) in the prevention of restenosis after percutaneous coronary intervention (PCI).

**Study Protocol**

Between March 1995 and May 1997, 70 patients who required coronary revascularization were registered in the present trial (Drug Delivery Device in Coronary Balloon Angioplasty Trial: 3D-CAT) at the National Cardiovascular Center. The 3D-CAT is a randomized controlled pilot trial for prevention of restenosis after coronary balloon angioplasty conducted at a single center. The inclusion criterion was that the patient was scheduled for elective POBA with a balloon size equal to or larger than 2.75 mm. All of the patients had ischemic chest pain or evidence of ischemia diagnosed by a thallium-201 or treadmill exercise test. The patients were randomly assigned to 2 groups
according to consecutive sealed envelopes; the control group (n=35) underwent a conventional method of POBA, and the argatroban group (n=35) had the addition of local delivery of argatroban. The exclusion criteria were (1) more than 80 years old or less than 20 years old, (2) a target lesion in a non-protected left main coronary artery, (3) a total occlusive lesion equal to TIMI 0-1 flow, (4) a severely calcified lesion, (5) a diffuse lesion, (6) a target vessel with severe proximal tortuosity, (7) a lesion that restenosed more than once, (8) a bypass graft vessel, (9) an indication for a new device (eg, directional coronary atherectomy, stent, rotational atherectomy or laser ablation), (10) poor left ventricular function (ejection fraction <40%), (11) patients receiving warfarin, (12) patients receiving an intravenous infusion of heparin, (13) a history of gastrointestinal bleeding, thrombocytopenia, or coagulopathy, (14) a history of stroke within the preceding 3 months, (15) acute myocardial infarction within the previous month, (16) patients undergoing thrombolysis within the past 24h, (17) pregnancy, and (18) other major illness including renal failure and liver dysfunction. Informed consent was obtained from each patient.

PCI Procedure and Adjunctive Therapy

Coronary angiography was performed using the Judkins method, and a bolus of 5,000–8,000 IU heparin was given intravenously after vascular access had been established. In the control group, the POBA was performed in a standard way with a bolus injection of heparin (50 U/kg per h) during the procedure, followed by an infusion of heparin (25 U/kg per h) for 4 h after the POBA. In the argatroban group, an intravenous infusion of argatroban was given (1μg/kg per min) 30 min before the POBA, followed by the local delivery of argatroban (10mg/20min) into the dilated site using the Dispatch™ catheter, and the postoperative treatment of intravenous infusion of argatroban for 4 h.
Local Delivery of Argatroban

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(CMS), Medical Imaging Systems Inc, Leiden, the Netherlands). CAG was performed before, immediately after, and 3 months after the POBA (follow-up) as described in detail elsewhere. All angiographic analyses were performed in a blinded fashion by an experienced physician. The % diameter stenosis (%DS) and minimal lumen diameter (MLD) of the target lesion were determined quantitatively. The diameter of a Judkins catheter was measured using a precision micrometer (No. 293-421-20; precision 0.001 mm, Mitutoyo Co, Kawasaki, Japan) to obtain a calibration factor in the ‘Free French’ mode in the image calibration of the CMS program. The calibration factor (CF) was adjusted between 0.08 and 0.1 mm/pixel using digital zoom according to the CMS manual. The complex edit mode (gradient field transform: GFT) was used in the case of a complex lesion, as described in detail elsewhere.

Angiographic restenosis after POBA was defined as a %DS greater than 50% on the follow-up angiogram. Clinical restenosis was defined as the recurrence of ischemia and/or target lesion revascularization within the period before the follow-up angiography.

Endpoints
The following endpoints were prospectively defined. Restenosis was the primary endpoint. Secondary endpoints included death, acute myocardial infarction (symptoms, ECG changes, and creatine kinase >twice the upper normal limit) and coronary revascularization (coronary bypass surgery, or repeated POBA and/or coronary stenting). Repeat revascularization of the target lesion was defined as angioplasty or bypass surgery performed because of restenosis of the target lesion in association with recurrent angina, objective evidence of myocardial ischemia, or both. The principal safety endpoints were abrupt vessel closure, stroke, major bleeding, or the need for vascular surgery. Major bleeding was defined as intracranial hemorrhage or overt bleeding associated with a decrease in hemoglobin of more than 5 g/dl.

Table 1 Baseline Clinical Characteristics of the Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=35)</th>
<th>Argatroban group (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61±8</td>
<td>61±8</td>
<td>NS</td>
</tr>
<tr>
<td>M/F</td>
<td>29/6</td>
<td>27/8</td>
<td>NS</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>23.6±2.0</td>
<td>23.5±2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>185±32</td>
<td>198±36</td>
<td>NS</td>
</tr>
<tr>
<td>Prior MI</td>
<td>13</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>57±10</td>
<td>58±13</td>
<td>NS</td>
</tr>
<tr>
<td>Diseased coronary vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>23</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD/LCX/RCA</td>
<td>18/13/4</td>
<td>16/16/3</td>
<td>NS</td>
</tr>
</tbody>
</table>

BMI, body mass index; MI, myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 2 Baseline Lesion Characteristics of the Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=35)</th>
<th>Argatroban group (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA classification</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A</td>
<td>5</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>B</td>
<td>29</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>De novo lesion</td>
<td>32 (94%)</td>
<td>28 (80%)</td>
<td>NS</td>
</tr>
<tr>
<td>Reference vessel diameter (mm)</td>
<td>2.89±0.46</td>
<td>2.89±0.39</td>
<td>NS</td>
</tr>
<tr>
<td>Minimal lumen diameter (mm)</td>
<td>0.86±0.24</td>
<td>0.83±0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>6.00±3.69</td>
<td>5.25±3.77</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccentricity</td>
<td>29 (83%)</td>
<td>27 (77%)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcification</td>
<td>12 (34%)</td>
<td>16 (46%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ostial lesion</td>
<td>4 (11%)</td>
<td>5 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Proximal tortuosity</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Angled lesion</td>
<td>4 (11%)</td>
<td>4 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>7 (20%)</td>
<td>6 (17%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Statistical Analyses
The data are presented as mean±SD (standard deviation). Differences in angiographical parameters (%DS and MLD) between the 2 groups before POBA, immediately after all procedure and during the follow-up were compared by unpaired t-test. Statistical comparisons of differences in categorical data between the 2 groups were performed using the chi-square test. Differences were considered significant when p<0.05. The clinical follow-up analyses were performed on an intention-to-treat basis and on-treatment-analeses. Moreover, angiographic follow-up analyses were performed using on-treatment-analeses.
Patient Population (Fig 1)
Four patients in the argatroban group were excluded from the follow-up CAG; 1 underwent stent implantation because of a major coronary dissection before the local delivery of argatroban, 1 had an abrupt vessel closure during the local delivery of argatroban, 1 required additional ballooning and stent implantation, and 1 refused to undergo the follow-up CAG with negative exercise thallium-201 stress imaging. Four patients in the control group were also excluded from the follow-up CAG: 3 required stent implantation because of major coronary dissection after the balloon angioplasty, and 1 had residual %DS >50% (angiographically unsuccessful). During the course of the study, 2 patients died suddenly (control 1, argatroban 1) before the follow-up angiography; the 1 in the argatroban group had cardiac sudden death after balloon angioplasty on day 60 (the patient had an old myocardial infarction with left ventricular dysfunction) and the patient in the control group died suddenly on day 60 after the balloon angioplasty (suspected rupture of a thoracic aortic aneurysm). In total, 10 patients (5 in each group) were excluded from the follow-up angiography.

Baseline Clinical and Lesion Characteristics
Tables 1 and 2 summarize the baseline clinical and lesion characteristics; there were no significant differences between the 2 groups in this study.

In-Hospital Outcome
The in-hospital outcomes are summarized in Table 3. An acute occlusion in the treated segment during the local delivery of argatroban using a Dispatch™ catheter was observed in 1 patient, requiring implantation of a Palmaz-Schatz stent. There were no major complications during the procedure in either group.

Quantitative CAG Analyses at Follow-up
Fig 2 compares the results of the angiographic analyses between the 2 groups. There were no significant differences between the 2 groups in % diameter stenosis or minimal lumen diameter immediately after PCI. Angiographic parameters including % diameter stenosis and minimal lumen diameter were marginally better in the argatroban group than in the control group at follow-up.

Restenosis Rates, Target Lesion Revascularization, and Clinical Follow-up Data
Fig 3 compares the restenosis rates in the 2 groups. The lesion restenosis (%DS >50%) rates were 27% in the argatroban group and 56% in the control group (p=0.02). The clinical restenosis rates were 14% in the argatroban group and 37% in the control group (intention-to-treat analysis; Table 4, p=0.03). The target lesion revascularization rates were 14% in the argatroban group and 34% in the control group.
group (intention-to-treat analysis; Table 4, p=0.05). Moreover, Table 5 shows the clinical outcome at follow-up of the study patients on-treatment-analysis. Seven cases (6 stent implantations and 1 unsuccessful procedure during initial angioplasty) were excluded in Table 5 according to on-treatment-analysis. The clinical restenosis rates at follow-up were 17% (n=5) in the argatroban group and 40% (n=12) in the control group according to on-treatment-analysis after exclusion of 10 cases (n=30, respectively; p=0.04). The details of those 10 cases are as follows: 6 stent implantations during procedure, 1 unsuccessful procedure, 2 deaths, and 1 refusal of follow-up CAG.

### Discussion

**Previous and Present Trials Regarding the Prevention of Restenosis**

No definitively effective prevention of restenosis by systemic administration of drugs has been observed in previous clinical trials. Several types of drug therapy, such as anticoagulants (heparin, warfarin) and antiplatelet therapy (aspirin, dipyridamole, ticlopidine, prostacyclin, and thromboxane A2 inhibitor), fish oil, and steroids have failed to reduce the restenosis rate in most clinical trials.22–24 Recently, trapidil and cholesterol-lowering agents have been shown to be promising in preventing restenosis after coronary angioplasty,25 but patients must take these drugs for several months after angioplasty.

In contrast, coronary stenting has been shown to be effective in preventing restenosis after coronary angioplasty.26,27 and the drug eluting stent has been developed in recent years.28 Nevertheless, adjunctive anticoagulation and/or antiplatelet therapy is required for 1 month after coronary stenting, resulting in occasional bleeding complications. Accordingly, a new procedure with a low rate of adverse effects and no need for adjunctive therapy after discharge has been sought. In the present randomized, controlled study, local delivery plus intravenous infusion of argatroban reduced both the angiographic and clinical restenosis rates after coronary angioplasty. There was no increase in bleeding risk with the argatroban treatment. The restenosis rate in the argatroban group in this trial (27%) was similar to that in the stent group of the STRESS trial (32%; NS),27 despite the fact that the reference vessel diameter was smaller (2.89±0.39 mm) than that in the STRESS trial (3.03±0.42 mm; p=0.07). The restenosis rate in the...
control group in the present study was similar to that in the control group of the CAVEAT trial (56% vs 57%).29

**Mechanism of Restenosis and Thrombin Activation**

The mechanism of restenosis after PCI is considered to be a healing process after a balloon injury. Immediately after arterial injury with a balloon catheter, many factors lead to the activation of medial smooth muscle cells (SMC), but there are three major ones. First, elastic recoil is a pivotal factor after mechanical trauma to the abnormal vessel wall and stretching of the normal vessel wall (ie, arterial remodeling). Second, the formation of thrombus on the intimal surface and inside the disrupted plaque is an important part of the restenosis process. The intensity of thrombus formation could serve to reduce the initial gain in lumen both by adding to the plaque mass and by elaborating more growth factors.30 Third, the most intense interest has been on the impact of mitogenic factors (basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and SMC-derived growth factor (SDGF)) released by platelets, monocytes, and by components of the intact parts of the vascular wall, including the SMC. In vitro and in vivo studies have shown that injury to the endothelium and the vessel wall causes increased thrombin production.31 Thrombin, in particular, may play a significant role in the initiation of the restenosis process, because the regulation of these growth factors has been reported to be modulated by thrombin via a thrombin receptor.32,33 Moreover, thrombin activates a variety of vascular and inflammatory cell types that promote wound healing.10,32 Thus, the inhibition of the initial thrombin activation may exert a potent preventative effect on restenosis after POBA.

**Direct Thrombin Inhibitors and Restenosis**

The direct thrombin inhibitors, such as r-hirudin, hirulog, hirugen and D-Phe-Pro-Arg-chloromethylketone (PPACK), are expected to reduce the restenosis rate after PCI11,34 and several relevant experimental studies have been performed in recent years. Rogasta et al reported that the 2-h systemic infusion of hirudin failed to reduce cell proliferation within the first 7 days, whereas the 2-h infusion of hirulog improved the late angiographic luminal diameter and reduced the cross-sectional area narrowing by plaque in rabbits compared with heparin controls after angioplasty. They suggested that (1) hirudin inhibits cellular migration rather than proliferation, and (2) hirudin reduces mural thrombosis, resulting in less thrombus incorporation into the plaque. However, Serruys et al reported that systemic administration of r-hirudin failed to reduce restenosis in a clinical study (HELVETICA study)35. This discrepancy between the experimental study (Rogasta et al12) and the clinical study (Serruys et al15) may be explained by a difference in the local concentration of hirudin at the target lesion. Accordingly, it is expected that the local delivery of a high concentration of a direct thrombin inhibitor using a drug delivery device would reduce restenosis without increasing adverse effects in the clinical setting. However, there has not a previous clinical prospective randomized trial using a direct thrombin inhibitor and a local delivery device for preventing restenosis after angioplasty.

The present study has demonstrated that the intracoronary local delivery of argatroban, in addition to a 4-h intravenous infusion, prevents restenosis following POBA. Argatroban has been reported to inhibit platelet activation by fibrin- or clot-incorporated thrombin more effectively than does hirudin16. The reason that both local delivery and continuous intravenous infusion of argatroban were used in the present study was to inhibit thrombin activity, which may increase immediately after angioplasty before the local delivery of argatroban, because there was a time delay (approximately 10 min) between the first balloon inflation and the local delivery of argatroban (thrombin receptors have been reported to appear on a SMC within a few min after balloon injury12). The present findings, together with the report of Rogasta et al13, suggest that direct thrombin inhibition may successfully inhibit cell migration in the initiation of restenosis in human patients.

**Local Drug Delivery Device**

Several local delivery balloon catheters have been designed. The double-balloon catheter was the first percutaneous drug delivery device. Other drug delivery devices such as the Wolinsky perforated-balloon catheter, a micro-porous balloon, a channel catheter, and the Transport coronary angioplasty catheter have been developed since then. More recently, the drug delivery devices known as the InfusasleeveTM, a hydrogel-coated balloon, and the DispatchTM catheter have become available.36 The hydrogel-coated balloon does not have a perfusion port to support distal blood flow during balloon inflation. Imanishi et al reported that the local delivery of argatroban using a hydrogel-coated balloon reduced intimal thickening after balloon injury in an experimental study.37 The DispatchTM catheter consists of an over-the-wire, non-dilatation catheter with a spiral inflation coil and a perfusion port on its distal tip. There are several advantages of this system for the drug delivery. First, this device allows distal coronary perfusion during balloon inflation for a sufficiently longer time compared with other drug delivery catheters. Second, this system makes it easier to deliver the drug than a hydrogel-coated balloon catheter, because in the case of the hydrogel-coated balloon, the drug must first penetrate the hydrogel-balloon surface. Third, the pharmacokinetic validity of the local delivery of argatroban using a DispatchTM catheter has been established. Anabuki et al confirmed that the local delivery of argatroban using a DispatchTM catheter resulted in the intramural deposition of high concentration argatroban without any arterial damage38. This new device has been used for the prevention of reocclusion after revascularization in patients with acute myocardial infarction and unstable angina pectoris18,39. However, there are no other clinical reports on the prevention of restenosis using the DispatchTM catheter except for one small non-randomized trial10. Thus, this is the first prospective randomized controlled trial using the DispatchTM catheter and argatroban to prevent restenosis following POBA. Moreover, it is expected that these local delivery devices may be available not only for direct thrombin inhibitor but also gene therapy in the future40.
obvious benefit of long-term inflation in preventing restenosis was found in a previous study\(^2\) the long-term inflation (20 min) with the Dispatch\textsuperscript{TM} catheter is unlikely to be responsible for the significant reduction of restenosis in the present study. Third, this trial was performed at a single center, with a small number of patients. Further study is necessary with a larger number of patients in a double-blind, randomized, multicenter trial with a placebo group (local delivery of normal saline using a Dispatch\textsuperscript{TM} catheter). We are now planning to conduct such a trial in Japan. Fourth, the effect of the exclusively local delivery of argatroban remains undetermined, because postoperative intravenous infusion of argatroban was combined with the intracoronary local delivery in the present study. Further study is necessary to assess the ‘pure’ efficacy of the local delivery of argatroban. Moreover, further study is necessary to assess the efficacy of stenting lesions in the present stenting era. Final, the present study did not evaluate local delivery of argatroban. Moreover, further study is necessary to assess the ‘pure’ efficacy of the local intravenous infusion of argatroban was combined with the study is necessary with a larger number of patients in a single center, with a small number of patients. Further inflation (20 min) with the Dispatch\textsuperscript{TM} catheter is unlikely to examine the local drug delivery pressure during infusion of argatroban in the clinical setting.

## Conclusions

The local delivery of argatroban using a Dispatch\textsuperscript{TM} catheter was observed to be safe and effective in preventing restenosis after balloon angioplasty.

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## References


