Late Angiographic Stent Thrombosis After Sirolimus-Eluting Stent Implantation

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Background Although drug-eluting stents dramatically reduce revascularization after percutaneous coronary intervention (PCI), it is still unclear whether they increase the risk of stent thrombosis. Late stent thrombosis (>30 days) was a very rare complication after bare metal stent implantation. Four cases of confirmed late angiographic stent thrombosis (LAST) after sirolimus-eluting stent (SES) implantation are presented and the incidence, promoting factors and outcomes of such cases in Japan, where clopidogrel has not been approved, are described.

Methods and Results Between September 2004 and March 2006, 725 patients underwent PCI with SES implantation and 679 patients (94%) were clinically followed up (median 271 days). There were 4 cases (0.6%) of LAST (at 60, 180, 215, and 508 days, respectively) after elective SES implantation resulting in myocardial infarction. Three cases occurred soon after antplatelet therapy discontinuation 3 patients died after LAST events. The incidence of LAST was 0.6%.

Conclusions LAST is a rare complication, even after SES implantation, at least in patients with appropriate antplatelet therapy. However, as it can lead to fatal complications, it must be taken into account, especially when antplatelet therapy is discontinued. (Circ J 2007; 71: 226–228)

Key Words: Antplatelet therapy; Drug-eluting stent; Late stent angiographic thrombosis; Sirolimus-eluting stent

Drug-eluting stents (DESs) reduce the need for repeat percutaneous intervention (PCI) compared with bare metal stents (BMSs), but there is concern about the increased risk of late stent thrombosis (>30 days) related to delayed endothelialization. Stent thrombosis usually results in ST-segment elevation myocardial infarction (MI) or death and in the era of DESs, late stent thrombosis may be a possible limitation of the procedure. In the international reports of late angiographic stent thrombosis (LAST) clopidogrel was used as the antplatelet therapy in most patients/studies. As antithrombotic therapies have a major impact on angiographic stent thrombosis after BMS or DES implantation, we wanted to evaluate the incidence, promoting factors and outcomes of LAST in Japan where clopidogrel has not been approved.

Methods

Study Patients A total of 725 patients (1,407 stents) with stable angina underwent successful elective sirolimus-eluting stent (SES) implantation between September 2004 and March 2006. Although several complex lesions, including in-stent restenosis, bifurcation, left main, and chronic total occlusion, were treated, SES were not implanted in any patients with acute coronary syndrome. A total of 679 patients (94%, 1,303 stents, 905 lesions) were clinically followed up (median follow-up 271 days).

Patients were pretreated with aspirin 200 mg/day and ticlopidine 200 mg/day at least 3 days prior to PCI and this therapy was continued for at least 3 months. The duration of antiplatelet therapy was left to the discretion of the attending physician. If a patient experienced adverse effects of ticlopidine (5.4%, 37 patients), cilostazol 200 mg/day was prescribed. We defined LAST as occurring more than 30 days after SES implantation.

Results There were 4 cases of LAST (Table 1) and the calculated incidence rate was 0.6% (95% confidence limit: 0.16–1.51). None of the patients on the antplatelet therapy of aspirin and cilostazol in combination developed LAST.

Case 1 A 65-year-old diabetic woman on chronic dialysis was admitted to hospital with chest discomfort in September 2004. Angiography showed a severe calcified narrowing at the bifurcation of the left anterior descending artery (LAD). She underwent PCI of the LAD. First, rotational atherectomy (Rotablator, Boston Scientific SciMed, USA) was performed on both lesions in the LAD (1.75 mm burr at 210,000 rpm) and in the diagonal branch (1.5 mm burr at 210,000 rpm). After balloon dilation of the lesion in the diagonal branch, a SES (Cypher®, Cordis, USA; 3.0 × 23 mm, 20 atm, 30 s) was placed in the LAD without any complication (Fig 1A). She was asymptomatic after PCI. In March 2005, both ticlopidine and aspirin were discontinued.
while she underwent biopsy of bladder cancer. Six days later (ie, 175 days after stenting) she was admitted to the emergency department with cardiogenic shock. Angiography revealed occlusion of the SES (Fig 1B), emergency PCI to this lesion was performed successfully, but the patient died 4 days later from multi-organ failure.

Case 2
In April 2005, a 75-year-old man was admitted to the hospital because of ECG abnormalities and angiography showed stenosis in the proximal segment of the LAD, requiring PCI. Predilation of the lesion was not sufficient to enable the SES to pass into the target lesion. After rotational atherectomy (Rotablator, Boston Scientific SciMed; 1.75 mm burr at 210,000 rpm), the SES (Cypher®; 3.0 x 28 mm 24 atm, 30 s) was placed in the LAD. The angiographic result was optimal. Sometime later, the patient developed an upper respiratory tract infection and stopped the antiplatelet therapy of both ticlopidine and aspirin, and 3 days later (ie, 45 days after SES implantation) he was admitted to the emergency department with chest pain. Emergency angiography showed total occlusion of the proximal site of the SES and although PCI was successful he was admitted to the emergency department with chest pain. Emergency angiography showed total occlusion of the proximal site of the SES and although PCI was successful he developed uncontrollable heart failure following this acute event and died 4 months later. 

Case 3
A 72-year-old diabetic man underwent coronary angiography to elucidate the etiology of heart failure in February 2005. A long diffuse narrowing in the LAD required PCI. After predilation with a balloon catheter, 2 SESs (Cypher®; 2.5 x 23 mm, 2.5 x 18 mm, 16 atm, 30 s) were implanted in the LAD. The proximal site of LAD showed haziness, and another SES (Cypher®; 2.5 x 18 mm, 16 atm, 30 s) was inserted. In September 2005, 210 days after SES implantation, he complained of chest pain at home and when the ambulance arrived, he was in ventricular fibrillation. Emergency angiography showed total occlusion with thrombus within the SES. Thrombolysis In Myocardial Infarction grade 3 flow was obtained after aspiration and the lesion was dilated with a balloon catheter. The procedure was successful but he died 3 days later from severe intractable heart failure. This patient was not known to have ceased the antiplatelet therapy.

Case 4
In October 2004, a 48-year-old man with a prior MI underwent PCI for a chronic total occlusion of the proximal LAD. After predilation, 3 SESs (Cypher®; 3.5 x 23 mm, 3.0 x 23 mm, 3.0 x 28 mm, 12 atm, 30 s) were successfully placed in the site of the lesion. His 8-month follow up coronary angiography showed no restenosis of the 3 SESs in June 2005. In March 2006, he presented at hospital with chest pain and was diagnosed with MI. He had stopped the antiplatelet therapy of his own volition more than 1 week prior to this event. Emergency angiography showed total occlusion just proximal to the site of the first SES. A BMS was successfully implanted instead of the SES and he was discharged from hospital uneventfully.

**Discussion**
We believe that this is the first report of LAST after SES implantation in Japan, where clopidogrel has not been approved and ticlopidine is used exclusively as the postoperative antiplatelet therapy. Antithrombotic therapy has a major impact on angiographic stent thrombosis after BMS and DES implantation,

<table>
<thead>
<tr>
<th>Patient</th>
<th>Days to LAST</th>
<th>Clinical outcome</th>
<th>Target lesion</th>
<th>Operative strategy</th>
<th>Antiplatelet therapy at time of LAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 F</td>
<td>180</td>
<td>CPA, dead</td>
<td>Proximal LAD</td>
<td>Rota, 3.0 x 23 mm</td>
<td>Aspirin and ticlopidine stopped 5 days prior</td>
</tr>
<tr>
<td>75 M</td>
<td>60</td>
<td>STEMI, dead</td>
<td>Proximal LAD</td>
<td>Rota, 3.0 x 28 mm</td>
<td>Aspirin and ticlopidine stopped 3 days prior</td>
</tr>
<tr>
<td>72 M</td>
<td>215</td>
<td>CPA, dead</td>
<td>LAD long lesion</td>
<td>2.5 x 29 mm</td>
<td>Aspirin and ticlopidine continuation</td>
</tr>
<tr>
<td>48 M</td>
<td>508</td>
<td>STEMI, alive</td>
<td>LAD CTO</td>
<td>3.5 x 23 + 3.0 x 21 mm</td>
<td>Aspirin and ticlopidine stopped 7 days prior</td>
</tr>
</tbody>
</table>

LAST, late angiographic stent thrombosis; CPA, cardiopulmonary arrest; LAD, left anterior descending; STEMI, ST-segment elevation myocardial infarction; CTO, chronic total occlusion.
factors and outcomes of LAST in patients on ticlopidine have not been evaluated.

LAST is extremely rare with BMS\textsuperscript{14,15} and its incidence with DES has been reported as 0.4–1.3\%\textsuperscript{16–21} In the present study it occurred in 0.6\% (95\% confidence limits 0.16–1.51) of the patient population who were treated with SES. LAST events may be a rare complication, even with DES, but they can be fatal, as ST-segment elevation MI occurred in 3 of the 4 patients.

The predictors of LAST with DES have not yet been completely elucidated. Cessation of antiplatelet therapy, renal failure, bifurcation lesions, diabetes and low ejection fraction, in-stent restenosis etc. have been reported\textsuperscript{16–21} All reports suggest that cessation of antiplatelet therapy contributes to LAST, but 1 of the present patients developed LAST while he was on dual antiplatelet therapy.

The mechanism of LAST has also not been established\textsuperscript{22,23} Intravascular ultrasound (IVUS) was not performed in the present patients because they were in a hemodynamically unstable condition, but we consider that IVUS may be helpful for discovering the etiology and mechanism of LAST. In 2 of the LAST patients rotational atherectomy was performed because of severe calcification and it is possible that there underexpansion or incomplete apposition of the stent.

In all of the cases, aspiration of the artery proved the existence of thrombus. Hypersensitivity or aneurysmal formation has been reported as a mechanism of LAST, but was not detected in the present patients.

The very low occurrence of LAST (4 cases (0.6\%)) is a limitation of this study. A larger study, such as the J-Cypher Registry, would be expected to reveal the causes, mechanisms and predictors of LAST.

In conclusion, LAST is not a common complication under appropriate antiplatelet therapy, but must be taken into account when patients treated with a DES need to stop antiplatelet therapy.

References


