Angioscopic Assessment of Early Phase Arterial Repair After Paclitaxel-Coated Nitinol Drug-Eluting Stent Implantation in the Superficial Femoral Artery

Takayuki Ishihara, MD; Osamu Iida, MD; Masaki Awata, MD, PhD; Kiyonori Nanto, MD; Shinsuke Nanto, MD, PhD; Masaaki Uematsu, MD, PhD

Background: Although durable clinical outcomes have been reported, arterial repair after paclitaxel-coated nitinol drug-eluting stent (Zilver PTX) implantation in the superficial femoral artery (SFA) remains unclear.

Methods and Results: Angioscopic evaluation was performed in SFA intra-stent surfaces 80±29 (range, 49–135) days or 84±18 (range, 52–112) days following Zilver PTX (20 stents in 10 patients; mean age, 72±8 years; 40% men) or bare metal stent (BMS; 14 stents in 9 patients; mean age, 70±7 years; 67% men) implantation, respectively. Neointimal coverage (NIC) was graded as 0, stent struts exposed; grade 1, struts bulging into the lumen, but still transparently visible although covered; grade 2, struts embedded in the neointima, but translucent; grade 3, struts fully embedded and invisible. NIC was defined as heterogeneous when the NIC grade variation was ≥1. Presence of yellow plaque and thrombus were investigated. Dominant NIC was significantly different between Zilver PTX (grade 0, 35%; grade 1, 20%; grade 2, 25%; grade 3, 20%) and BMS (grade 0, 7%; grade 1, 0%; grade 2, 14%; grade 3, 79%; P=0.001). NIC heterogeneity was less frequently observed in Zilver PTX (40% vs. 86%, P=0.009). Prevalence of yellow plaque or thrombus (75% vs. 79%, P=0.57) or thrombus (75% vs. 79%, P=0.57) were similar between Zilver PTX and BMS.

Conclusions: Early phase arterial repair was different between Zilver PTX and BMS. (Circ J 2013; 77: 1838–1843)

Key Words: Angioscopy; Drug-eluting stent; Peripheral artery disease

Endovascular therapy is being performed with increasing frequency for the treatment of peripheral artery disease (PAD). In particular, in the treatment of lesions in the femoropopliteal artery, nitinol stent implantation is associated with better clinical outcome as compared to balloon angioplasty, with a primary patency rate of around 60–80%.1–5 Recently paclitaxel-coated nitinol drug-eluting stents (Zilver PTX; Cook Medical, Bloomington, IN, USA) have become available for the treatment of patients with femoropopliteal PAD, and durable clinical outcomes have been reported.6,7 Although in the treatment of coronary artery disease, drug-eluting stents (DES) have successfully decreased the rate of in-stent restenosis and target lesion revascularization by inhibiting neointimal proliferation,8–10 their safety has been limited by occurrence of late stent thrombosis (LST) and very LST (VLST) >1 month after DES implantation in association with sudden death or myocardial infarction.11–13 In the treatment of PAD, a study reported a frequency of subacute stent thrombosis of 2.0% after bare metal stent (BMS) implantation,1 but there are no published data on stent thrombosis for DES, and the safety in this setting has not been well investigated.

Angioscopy directly visualizes arterial healing following stenting.14–20 In this study, we examined the arterial repair after Zilver PTX implantation in the superficial femoral artery (SFA) using angioscopy.

Methods

Patients
This was a prospective and single-center study consisting of 19 patients with PAD (mean age, 71±8 years; 53% male). Stent selection was decided based on availability. Zilver PTX became available in July 2012. Therefore, before July 2012, 14 BMS were implanted in 9 lesions in 9 patients. After June 2012, 20 Zilver PTX stents were deployed in 10 lesions in 10 patients. All patients agreed to receive follow-up angioscopy as well as angiography 2–4 months after stent implantation (Zilver PTX,
Arterial Repair Following Zilver PTX in the SFA

**Definition of NIC grade**

NIC was graded as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>stent struts exposed</td>
</tr>
<tr>
<td>1</td>
<td>struts bulged into the lumen, although covered</td>
</tr>
<tr>
<td>2</td>
<td>struts embedded by the neointima, but translucent</td>
</tr>
<tr>
<td>3</td>
<td>struts fully embedded and invisible</td>
</tr>
</tbody>
</table>

Figure 1. Definition of neointimal coverage grade: grade 0, stent struts fully visible, similar to immediately after implantation; grade 1, stent struts bulging into the lumen and, although covered, still clearly visible; grade 2, stent struts visible, but not clearly seen; grade 3, stent struts not visible on angioscopy.

40±29 days; BMS, 84±18 days; P=0.61). We compared angiographic findings between Zilver PTX and BMS.

**Angiographic and Angioscopic Follow-up**

Peripheral angiography was performed after unfractionated heparin (5,000 IU) was given into the brachial or femoral artery via the inserted sheath. Subsequently, angioscopy was conducted using Vecmova NEO (FiberTech, Tokyo, Japan). Detailed angioscopy product specifications and procedures have been described elsewhere. Briefly, the optical fiber was placed at the distal segment of the peripheral artery and was manually pulled back from the distal to the proximal stent edge under careful angioscopic and angiographic guidance. Angioscopic images consisted of 3,000 full-color pixels and were stored on digital videotapes for off-line analysis.

**Angioscopic Analysis**

Angioscopic images were analyzed for the following: (1) dominant degree of neointimal coverage (NIC) over the stent; (2) heterogeneity of NIC; (3) existence of thrombus; and (4) existence of yellow plaque (YP) underneath the stent. NIC over the stent was classified into 4 grades as previously described for the coronary artery (Figure 1). Grade 0 was defined as stent struts fully visible, similar to immediately after implantation. Grade 1 was defined as stent struts bulging into the lumen and, although covered, still clearly visible. Grade 2 was defined as stent struts visible, but not clearly seen. Grade 3 was defined as stent struts not visible on angioscopy. NIC was evaluated through the entire stented segment, and judged as heterogeneous if NIC ranged across ≥1 grade. Struts that crossed the side branch were excluded from grading because they all had grade 0 regardless of stent type. The stent edges were also excluded from the heterogeneity analysis. Stent overlapped segments were also evaluated separately. Thrombus was defined based on the criteria adopted by the European Working Group on Coronary Angioscopy. The angioscopic definition of YP was adopted from the earlier reports, and the existence of YP underneath the stent was evaluated.

**Statistical Analysis**

All results are expressed as mean±SD unless otherwise stated. Continuous variables with homogeneity of variance were analyzed using Student’s t-test and those without it were analyzed using Welch t-test. Categorical variables were analyzed with Fisher’s exact test for 2×2 comparisons. For more than 2×2 comparisons, Mann-Whitney test was used. Statistical significance was defined as P<0.05. All calculations were performed using IBM SPSS Statistics version 20 (IBM, Armonk, New York, USA).

**Results**

**Patients**

Patient characteristics were equally distributed between the Zilver PTX and BMS groups (Table 1). In lesion and procedural characteristics, stent diameter was larger in the BMS group (P=0.0070) and stent length was longer in the Zilver PTX group (P=0.018; Table 2). Medication use is listed in Table 3; there were no differences between the Zilver PTX and BMS groups (Table 3).

**Angioscopic Findings**

Dominant NIC in the Zilver PTX stents was almost equally distributed from grade 0 to grade 3. In contrast, >90% of BMS...
had grade 2 or grade 3 dominant NIC. Dominant NIC grade was significantly different between the Zilver PTX and BMS groups (Figure 2). Within each stent, Zilver PTX had significantly less heterogeneity of NIC than BMS (Figure 3; P=0.006). All the thrombi detected on angioscopy were mural and subclinical. Existence of thrombus was not different between Zilver PTX and BMS (75% vs. 79%, P=0.57). All thrombi were red thrombi. Prevalence of YP also was not different between the 2 groups (75% vs. 79%, P=0.57). Representative cases are shown in Figure 4.

### Discussion

The main findings of this study were: (1) the distribution of dominant NIC grade was significantly different between Zilver PTX and BMS; (2) Zilver PTX had less NIC heterogeneity than BMS; and (3) prevalence of thrombus and YP was simi-
Similar to the report on coronary arteries, BMS implanted in the SFA had sufficient dominant NIC and high heterogeneity 2–4 months after stenting in the present study. In contrast, due to the effect of inhibiting neointimal proliferation, arterial repair was insufficient through the broad stented area, which resulted in low-grade NIC and high homogeneity after Zilver PTX implantation.

Thrombus and YP were observed in approximately 80% of both groups. A previous study showed that thrombus adhesion was an initial phase of neointimal proliferation.\textsuperscript{24,25} Other studies also noted that angioscopy-detected YP was covered by neointima 6 months after BMS implantation.\textsuperscript{14,22} Therefore, judging from the present result for thrombus and YP, the SFA is still in the process of arterial repair 2–4 months after stent implantation between them.

On angioscopic observation of the coronary artery, we have previously found that the dominant NIC grade ranged mostly from grade 0 to 1 approximately 4 months after sirolimus-eluting stent implantation, while all stents had grade 2–3 dominant NIC coverage after BMS implantation.\textsuperscript{18,19} In this study, on artery repair of SFA, similar results were obtained compared with those in the coronary artery tree.

Ueda et al reported on the angioscopic findings of BMS implanted in the coronary artery, and found that 65–142 days after BMS implantation all stents were covered by neointima while some stent struts were translucent.\textsuperscript{23} In other words, grade 3 NIC was not apparent in the whole stented area at this phase, which suggested that artery repair was still ongoing.

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Implantation.

Clinical Implication
The recommended duration of dual anti-platelet therapy (DAPT) is 2 months because the paclitaxel elutes for 56 days in Zilver PTX. A ratio of uncovered struts to total stent struts per section >30% has been found to be a risk factor for stent thrombosis in coronary arteries. The present study identified incomplete arterial repair 2–4 months after Zilver PTX implantation with associated risk of stent thrombosis. This finding suggests the need for continuation of DAPT beyond 2 months after Zilver PTX implantation in the SFA.

It has been reported that delayed arterial healing and abnormal vascular response are due to the polymer in DES, which could underlie LST and VLST in coronary arteries. Moreover, LST and VLST persistently occur with a cumulative incidence of 0.26–0.53%/year. In contrast to coronary DES, Zilver PTX has no polymer, which suggests a low risk of LST and VLST. Lifelong continuation of DAPT is thought to be unnecessary, but further investigation is necessary to decide the optimal duration of DAPT.

Study Limitations
This study contained several important limitations. First, fluoroscopic evaluation of the entire stented segment was on occasion not possible. Both stent length and the degree of blood flow from the side branch or distal artery affect fluoroscopic assessment. Angioscopic evaluation was performed only in the segment where an adequate image could be obtained, rendering it not possible to generalize the ratio of the observed to the non-observed length in the stent. Second, for stents implanted in the peripheral artery, the definition and frequency of stent thrombosis have not been clarified as yet. Moreover, the exact relationship between angioscopic evaluation and stent thrombosis is also unclear for the peripheral artery territory. Further investigation is necessary. Finally, this study was a single-center, small, and non-randomized observation study of intrastent surfaces on angioscopy.

Conclusions
Early phase arterial repair was different between Zilver PTX and BMS. Continued arterial repair was apparent 2–4 months after Zilver PTX implantation in the SFA.

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Disclosures
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References