The International Journal of Cardiovascular Imaging (2019) 35:1777–1784
https://doi.org/10.1007/s10554-019-01638-1

ORIGINAL PAPER

Vascular response to paclitaxel-eluting nitinol self-expanding stent in superficial femoral artery lesions: post-implantation angioscopic findings from the SHIMEJI trial (Suppression of vascular wall Healing after IMplantation of drug Eluting peripheral stent in Japanese patients with the Infra inguinal lesion: serial angioscopic observation)

Yoshiro Tsukiyama[1] · Toshiro Shinke[1,8] · Takayuki Ishihara[2] · Hiromasa Otake[1] · Daisuke Terashita[1] · Amane Kozuki[3] · Masashi Fukunaga[4] · Kan Zen[5] · Tetsuo Horimatsu[4] · Kenichi Fujii[4] · Junya Shite[3] · Masaaki Uematsu[2] · Mitsuyoshi Takahara[6] · Osamu Iida[2] · Shinsuke Nanto[7] · Ken-ichi Hirata[1]

Received: 18 January 2019 / Accepted: 27 May 2019 / Published online: 14 June 2019

Abstract

The aim of this study was to elucidate the vascular responses to paclitaxel-eluting stent (Zilver PTX stent) in superficial femoral artery lesion at different elapsed times using angioscopy. Patients who received Zilver PTX stent implantation from five centers were enrolled. We performed angioscopic examinations at 2, 6, and 12 months after implantation and evaluated neointimal coverage (NIC) grade, intra-stent thrombus (IS-Th) grade, and presence of yellow plaque. NIC grade 0 was defined as stent struts exposed; grade 1, struts transparently visible although covered; grade 2, struts embedded in the neointima, but translucent; and grade 3, struts fully embedded and invisible. IS-Th was graded as follows: grade 0 (none), 1 (focal), and 2 (diffusely spread). Angioscopic follow-up evaluation was performed at 2 months (25 patients, 42 lesions), 6 months (18 patients, 23 stents), and 12 months (14 patients, 24 stents) after stent implantation. Dominant NIC grade significantly increased over time; however, 16.3% of the cases had NIC grade 1 or 2 at 12 months. IS-Th grade decreased; however IS-Th and yellow plaque were persistently observed in 62.5% and 83.3% cases, respectively, at 12 months. An ongoing healing response was observed at 12 months after implantation; however, thrombogenic findings were noted. Prolonged dual antiplatelet therapy could potentially enhance the clinical utility of Zilver PTX.

Keywords Zilver PTX · Intra-stent thrombus · Neointimal coverage · Angioscopy · Superficial femoral artery · Stent thrombosis

✉ Toshiro Shinke
shinke@med.showa-u.ac.jp

1 Kobe University Graduate School of Medicine, Kobe, Japan

2 Kansai Rosai Hospital, Amagasaki, Japan

3 Osaka Saiseikai Nakatsu Hospital, Osaka, Japan

4 Hyogo College of Medicine, Nishinomiya, Japan

5 Omihachiman Community Medical Center, Shiga, Japan

6 Osaka University Graduate School of Medicine, Osaka, Japan

7 Nishinomiya Municipal Central Hospital, Nishinomiya, Japan

8 Division of Cardiovascular Medicine, Showa University School of Medicine, 1-5-8, Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan

Introduction

Endovascular therapy (EVT), including percutaneous transluminal balloon angioplasty (PTA) and bare metal stent (BMS) implantation, has been commonly performed for the treatment of patients with symptomatic peripheral artery disease (PAD). However, particularly in superficial femoral artery (SFA) disease, PTA and BMS implantation have not achieved satisfactory clinical outcomes.

Paclitaxel-coated nitinol drug-eluting stents (Zilver PTX; Cook Medical, Bloomington, IN, USA) was approved for the treatment of SFA disease. Zilver PTX stent has demonstrated improved patency compared with PTA or BMS in SFA lesions [1–3]. However, delayed vascular healing after Zilver PTX stent implantation, which could result in late

stent thrombosis (ST), remains a critical issue. ZEPHYR Registry reported that the ST incidence at 1 year was 2% among 831 lesions [4]. Moreover, previous autopsy studies reported that a delayed healing response characterized by delayed strut coverage, great thrombus attachment, and intra-stent neoatherosclerosis has been identified as the main mechanism of late and very late ST following percutaneous coronary intervention (PCI) [5–7].

Angioscopy is an imaging modality that visualizes intravascular features following stenting and enables monitoring of vascular responses in the coronary artery. Recently, angioscopy has emerged as an alternative tool for the evaluation of vascular response to stent placement in SFA lesions [8].

To reduce the risk of ST, continuation of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for at least 2 months has been the standard care after Zilver PTX stent placement as recommended by the Japanese Health, Labor, and Welfare Ministry, especially that precise vascular healing process has yet to be established. Consequently, most ST cases developed 3 months after Zilver PTX stent implantation [4]. In addition, delayed onset and inter-patient response variability were identified as drawbacks in DAPT using clopidogrel [9–11], and high residual platelet reactivity due to clopidogrel resistance has been reported to be a potential risk for ST after PCI [12, 13]. However, the effect of clopidogrel resistance on thrombosis after EVT remains unknown.

Thus, this prospective study aimed to elucidate the time course of vascular healing following Zilver PTX stent implantation in the SFA using angioscopy.

Methods

Patient population

The SHIMEJI (Suppression of vascular wall Healing after IMplantation of drug Eluting peripheral stent in Japanese patients with the Infra-inguinal lesion: serial angioscopic observation) study is a multi-center prospective observational registry designed to elucidate vascular responses to Zilver PTX stent implantation in the SFA at different elapsed times using angioscopy. Patients who had successful Zilver PTX implantation in the SFA in five centers (Kobe University Graduate School of Medicine, Kansai Rosai Hospital, Osaka Saiseikai Nakatsu Hospital, Hyogo College of Medicine, and Omihachiman Community Medical Center) between August 2013 and December 2015 were registered.

The patients received angioscopic examinations at 2, 6, or 12 months after Zilver PTX stent implantation to assess vascular healing status at each time point. Allocation of the timing of angioscopic examination was according to operator and institutional discretion. Moreover, the patients received DAPT with clopidogrel 75 mg once daily (od) and aspirin 100 mg od, which were started before Zilver PTX stent implantation; the same regimen was continued until the follow-up angioscopy.

Exclusion criteria of this registry were (1) stents placed above the SFA origin or below the medial femoral epicondyle; (2) anatomically unsuitable target artery for angioscopic evaluation; (3) use of oral anticoagulants; (4) pregnant women, breast-feeding patients, or scheduled pregnancies; (5) history of allergies to aspirin or clopidogrel; and (6) no written informed consent from the patient. In-stent restenosis was included in this study.

EVT procedure and angioscopic image acquisition

Catheterization was performed via a brachial or femoral approach using ≥ 6F catheters after intravenous administration of 5000 U unfractionated heparin. EVT was performed under angiography or intravascular ultrasound guidance, according to institutional standard practice. Zilver PTX implants were placed at least 1 cm below the SFA origin and above the medial femoral epicondyle to fully cover the target lesions. Pre-dilation and post-dilation were at the physician's discretion; residual stenosis < 30% was required for procedural success.

Angioscopy was performed at 2, 6, or 12 months after Zilver PTX stent implantation using FULLVIEW NEO (FiberTech, Tokyo, Japan) to evaluate the vascular responses. Detailed specifications and procedures of angioscopy were as previously described [14, 15]. 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 observations of the stented lesions were performed while blood was cleared away from the viewing area by administering 3% dextran-40 through the probing catheter. Angioscopic images consisted of 3000 full-color pixels and were stored on digital videotapes for off-line analysis.

Angioscopic image analysis

All images were digitally stored and submitted to a core laboratory for independent evaluation (CardioPort, Osaka, Japan). For image quality assessment, lesions were classified as analyzable when half of the whole cross-section within the stented segment was visible. Angioscopic images were analyzed for the following: (1) dominant neointimal coverage (NIC) over the stent (NIC grade) (2) expansion of thrombus over the stented lesion (IS-Th grade), and (3) existence of yellow plaque (YP) underneath the stent.

NIC over the stent was semi-quantitatively graded from 0 to 3, as previously described for coronary artery [16–18].

Grade 0 means that stent struts was exposed, similar to that immediately after stent implantation; grade 1 means that stent struts were bulging into the lumen and, although covered, still clearly visible; grade 2 means that stent struts were embedded by neointima but still translucent; and grade 3 was defined as stent struts not visible on angioscopy. Stent struts on the side branch were excluded from NIC grading.

The angioscopic definition of thrombus in stented segment (IS-Th), i.e., a white or red material that had cotton-like or ragged appearance or that presented fragmentation with or without protrusion into the lumen or adherent to the luminal surface, was based on the criteria by the European Working Group on Coronary Angioscopy [19]. IS-Th was graded from 0 to 2. Grade 0 means no thrombus over the stented segment, grade 1 means spotty thrombus or several spotty thrombi, and grade 2 means thrombus extended over the strut.

YP was defined simply as the yellow area on the luminal surface, which may have a smooth or irregular surface with or without protrusion into the lumen [14, 15, 20], and the existence of YP underneath the stent was evaluated.

All angioscopic images were analyzed by two independent investigators blinded to patient information (T. I. and O.I.). In case of disagreement, a consensus reading was obtained from a third independent investigator (T.S.).

Platelet function test

We obtained blood samples from the arterial sheath at the follow-up phase (2, 6, or 12 months after Zilver PTX stent implantation) and assessed residual platelet reactivity using VerifyNow® point-of-care P2Y12 assay (Accumetrics Inc., San Diego, CA, USA) to determine the relationship between in-stent response and residual platelet reactivity.

Study endpoints

The primary endpoints of the study were dominant NIC grade and expansion of thrombus over the stented lesion (IS-Th grade). The secondary endpoint included the existence of YP underneath the stent.

In-stent restenosis was defined as recurrence of 50% diameter stenosis determined by angiography or a peak systolic velocity ratio > 2.4 by DUS. Target lesion revascularization and requirement of major amputation (defined as surgical limb excision above the ankle) were recorded. All deaths were considered cardiac-related unless an unequivocal noncardiac cause could be established. Stent thrombosis was determined when apparent occlusion met the following criteria: (1) initial procedural success; (2) rapid symptom occurrence; (3) thrombus present at procedure; and (3) lesion resolved with < 50% diameter narrowing by thrombolysis therapy.

Statistical analysis

Statistical analyses were conducted using SPSS software version 24 (IBM Corp., Armonk, NY, USA). Qualitative data are presented as frequencies, and quantitative data are shown as mean values ± standard deviation. For continuous variables, comparisons between two groups were performed using a two-tailed, unpaired t-test or Wilcoxon test. Discrete variables are presented as percentages, and comparisons were performed by chi-square analysis or Fisher's exact test. At each step, the least significant variable was discarded from the model until all variables in the model reached a p value of < 0.20. A p value < 0.05 was considered statistically significant.

The association of elapsed time with intra-stent thrombus and with neointimal coverage was analyzed using the generalized linear mixed model with a cumulative logit link function, while that with the presence of YP was analyzed using the generalized linear mixed model with a binomial logit link function. In these models, the inter-subject variability was treated as random effects; the elapsed time, as fixed effects. Statistical analysis was performed by R version 3.1.0 (R Core Team, Vienna, Austria).

Moreover, we also used the generalized linear mixed model with a cumulative logit link function to investigate the effect of platelet reactivity units (PRU) on intra-stent thrombus with adjustment for elapsed time.

Results

Clinical and patient characteristics

Between August 2013 and December 2015, 63 patients with 101 lesions were enrolled in this study. After excluding poor angioscopy images, 25 patients with 42 lesions at 2 months, 18 patients with 23 lesions at 6 months, and 14 patients with 24 lesions at 12 months after Zilver PTX implantation were eligible for angioscopic evaluation.

Baseline patient clinical characteristics are shown in Table 1. No significant differences in age, body mass index, lipid profile, or clinical status between the three groups were found. The number of males was significantly lower in the 12 months follow-up group.

Procedural and lesion characteristics

Procedural and lesion characteristics are presented in Table 2. No significant difference in procedural and lesion characteristics was noted. Symptomatology justifying treatment was intermittent claudication of the lower limbs (2 months follow-up arm, 96.0%; 6 months follow-up arm, 94.4%; and 12 months follow-up arm, 92.9%) and critical

Table 1 Baseline patients characteristics

Variable	2 months f/u (n = 25)	6 months f/u (n = 18)	12 months f/u (n = 14)	p value
Age	74 ± 9	70 ± 11	76 ± 6	0.24
Male, n (%)	18 (72.0)	15 (83.3)	6 (42.9)	0.044
BMI (kg/m^2)	22.7 ± 3.6	21.5 ± 3.4	23.3 ± 4.0	0.36
Diabetes mellitus, n (%)	15 (60.0)	10 (55.6)	12 (85.7)	0.16
Hypertension, n (%)	23 (92.0)	16 (88.9)	14 (100)	0.46
Dyslipidemia, n (%)	17 (68.0)	14 (77.8)	9 (64.4)	0.43
Smoker, n (%)	8 (32.0)	5 (27.8)	1 (7.1)	0.19
Coronary artery disease, n (%)	11 (44.0)	8 (44.4)	9 (64.4)	0.43
Medication				
Statin	15 (60.0)	10 (55.6)	9 (64.3)	0.88
Cilostazol	1 (4.0)	8 (44.4)	4 (28.6)	0.004
Symptoms				0.44
Claudication, n (%)	24 (96.0)	17 (94.4)	13 (92.9)	
Critical limb ischemia, n (%)	1 (4.0)	1 (5.6)	1 (7.1)	

Values are presented as means ± SD or percentages

BMI: body mass index

Table 2 Limb and lesion characteristics

Variable	2 months f/u (n = 25)	6 months f/u (n = 18)	12 months f/u (n = 14)	p value
Number of lesions, n	42	23	24	NA
Elapsed time, days	75 ± 16	235 ± 53	385 ± 69	< 0.001
CTO, n (%)	20 (80.0)	10 (55.6)	10 (71.4)	0.21
Calcification lesion, n (%)	11 (44.0)	13 (72.2)	10 (71.4)	0.12
Number of Zilver PTX per lesion, n (%)	1.9 ± 0.9	1.6 ± 0.6	1.8 ± 0.8	0.57
Total length of Zilver PTX per lesion, mm	167 ± 93	137 ± 88	175 ± 97	0.53
Direct stenting, n (%)	7 (28.0)	2 (11.1)	0 (0.0)	0.057
Post dilation, n (%)	25 (100.0)	18 (100.0)	14 (100.0)	–

Values are presented as means ± standard deviations or percentages

CTO: chronic total occlusion

ischemia (2 months follow-up arm, 4.0%; 6 months follow-up arm, 5.6%; and 12 months follow-up arm, 7.1%); no statistically significant difference was observed (p = 0.44).

No difference in the total length of stented lesions (2 months follow-up arm, 167 ± 93; 6 months follow-up arm, 137 ± 88; and 12 months follow-up arm, 175 ± 97; p = 0.53) and in the number of Zilver PTX per lesion (2 months follow-up arm, 1.9 ± 0.9; 6 months follow-up arm, 1.6 ± 0.6; and 12 months follow-up arm, 1.8 ± 0.8; p = 0.53) were found.

Study endpoints

Angioscopic findings are shown in Figs. 1, 2, and 3. A significant increase in dominant NIC grade from 2 to 6 months (p < 0.001) and from 2 to 12 months after stent implantation (p < 0.001) was found. However, improvement in NIC grade from 6 to 12 months was poor. At 12 months, 16.3% of the cases had NIC grade 1 or 2 (Fig. 1).

The IS-Th grade from 2 to 6 months tended to improve (p = 0.096), and a significant improvement from 2 to 12 months after stent implantation was found (p = 0.033). However, IS-Th was still observed in 69.6% and 62.5% of the cases at 6 and 12 months, respectively (Fig. 2). YP was persistently observed over time in 83% of the cases at 12 months (Fig. 3). Representative cases are shown in Fig. 4.

Platelet function test

The median PRU value was 167 ± 93 at 2 months, 137 ± 88 at 6 months, and 175 ± 97 at 12 months. The adjusted odds ratio of PRU for intra-stent thrombus was 1.4 (95% CI 0.9–2.2) per 50-point increase (p = 0.101).

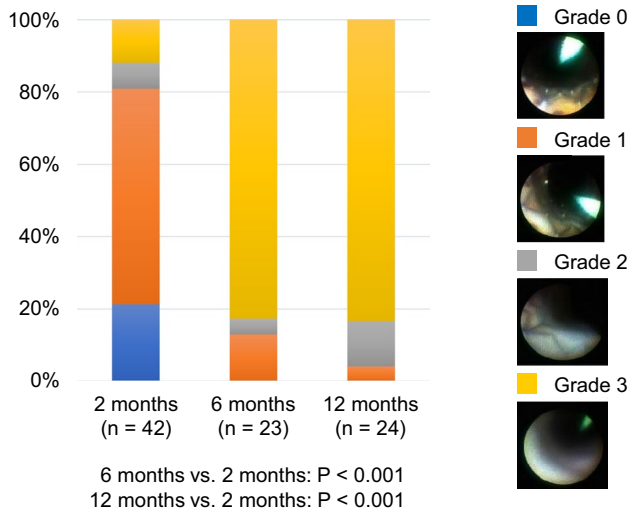

Fig. 1 Dominant NIC grade. NIC gradually improved over time; however, NIC improvement was poor from 6 to 12 months. *NIC* neointimal coverage

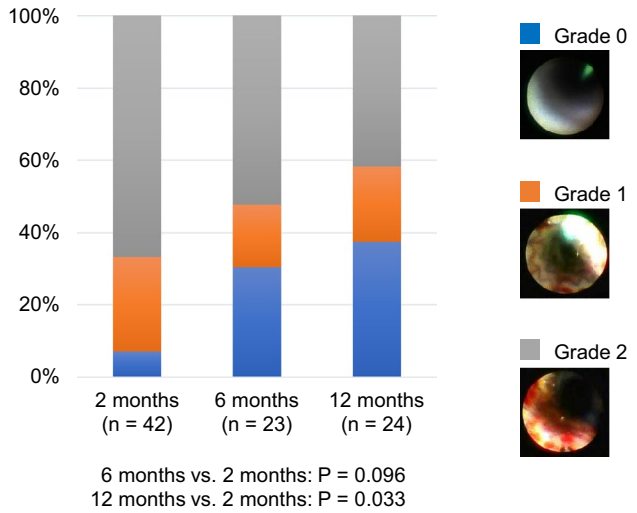

Fig. 2 IS-Th grade. IS-Th grade decreased over time; however, the incidence of IS-Th remained more than half even at 6 and 12 months. *IS-Th* intra-stent thrombus

Clinical outcomes

Clinical events within 12 months after Zilver PTX stent implantation, death, major amputation, stent thrombosis, in-stent restenosis and target lesion revascularization, were described in Table 3. There was no significant difference among the three groups.

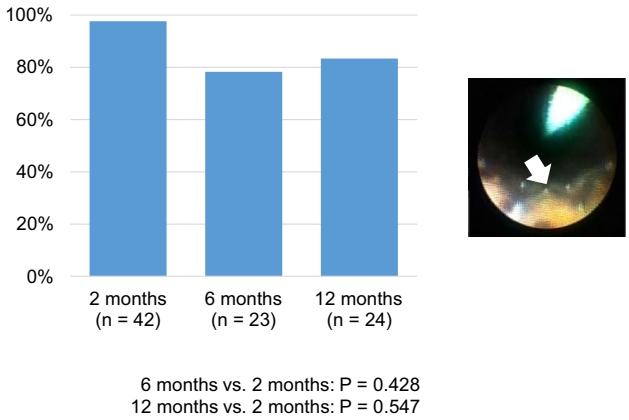

Fig. 3 Presence of yellow plaque. Yellow plaque was persistently observed over time (83% of the cases even at 12 months)

Discussion

In this study, angioscopic examination after Zilver PTX stent implantation was performed and revealed the following: (1) dominant NIC grade significantly increased over time; however, 16.3% of the cases had NIC grade 1 or 2 even at 12 months; (2) IS-Th decreased; however, IS-Th was still observed in 62.5% of the cases even at 12 months; (3) YP was persistently observed over time and was noted in 83% of the cases at 12 months; and (4) thrombus over the stented lesion tended to expand as the PRU increased.

Previous autopsy studies reported that an uncovered strut and IS-Th are risk factors for late ST and very late ST after PCI using a drug-eluting coronary stent [6, 7]. A direct full-color observation of the vascular wall is possible with angioscopy; thus, angioscopy is a robust tool to assess vascular healing after stent placement in coronary artery disease [14–17, 19, 21, 22]. A ratio of uncovered struts to total stent struts per section of > 30% has been considered a risk factor for ST in coronary artery disease [7]. Angioscopic observation of the coronary artery showed that the dominant NIC grade was grade 0–1 at approximately 4 months after sirolimus-eluting stent implantation, and the dominant NIC grade was grade 2–3 after BMS implantation [16, 17].

An angioscopic evaluation after the treatment of SFA lesions demonstrated that > 90% of BMS had grade 2- or 3-dominant NIC at 2–4 months after stent implantation [8]. In our study, Zilver PTX stent had insufficient stent coverage (grade 2 or grade 3 in approximately 20% of the cases) at 3 months. The dominant NIC grade of Zilver PTX stent was similar to that of BMS at 6–12 months after implantation (grade 2 or grade 3 in approximately 90% of the cases). These results showed that the NIC after Zilver PTX implantation is delayed compared with BMS.

Moreover, IS-Th was observed in approximately 60% and YP in approximately 80% of the cases even at 12 months in

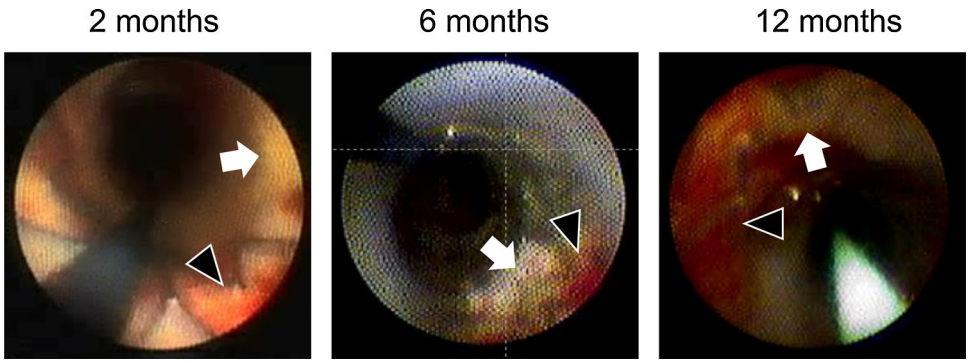

Fig. 4 Representative angioscopic findings at 2, 6, and 12 months after Zilver PTX stent implantation. Angiographic findings at the 2-month follow-up (left), 6-month follow-up (middle), and 12-month follow-up (right). Angioscopy at the 2-month follow-up showed exposed stent strut (NIC grade 0), thrombus (black arrowhead) extended over the strut (IS-Th grade 2), and the presence of YP (white arrow). Angioscopy at the 6-month follow-up showed transparently visible but covered stent strut (NIC grade 1), several spotty thrombi (IS-Th grade 1), and the presence of YP. Angioscopy at the 12-month follow-up showed struts embedded in the neointima but were translucent (NIC grade 2), several spotty thrombi (IS-Th grade 1), and the presence of YP. *NIC* neointimal coverage, *IS-Th* intra-stent thrombus, *YP* yellow

Table 3 Clinical events within 12 months after Zilver PTX stent implantation

Variable	2 months f/u (n = 25)	6 months f/u (n = 18)	12 months f/u (n = 14)	p value
Death	0 (0.0)	0 (0.0)	0 (0.0)	–
Major amputation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Stent thrombosis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
In-stent restenosis, n (%)	0 (0.0)	3 (16.7)	2 (14.3)	0.067
TLR, n (%)	0 (0.0)	3 (16.7)	1 (7.1)	0.071

Values are presented as means ± SD or percentages

TLR target lesion revascularization

this study. A previous optical coherence tomography (OCT) study showed an independent association of uncovered struts with late ST, and angioscopic studies reported that YP is an important contributing factor to very late ST [23–26]. Moreover, the presence of IS-Th and YP has been considered an initial phase of neointimal formation [14, 20, 27, 28]. Hence, this study demonstrated that arterial repair after Zilver PTX stent is ongoing even at 12 months after stent implantation.

To reduce the risk of ST, DAPT with aspirin in combination with clopidogrel has been the standard care after Zilver PTX stent implantation. The recommended DAPT duration after Zilver PTX stent implantation is 2 months, given that paclitaxel elutes for 56 days in Zilver PTX [2]. However, this recommendation is not supported by sufficient clinical data and evidence. In the ZEPHYR Registry, almost all cases of ST developed 3 months after Zilver PTX stent implantation [4]. Thus, a longer DAPT duration, i.e., > 2 months, after Zilver PTX stent implantation in SFA lesion may be necessary. Furthermore, based on the current findings for uncovered strut, IS-Th, and YP, the optimal DAPT duration after Zilver PTX stent implantation might be > 12 months.

The anti-platelet potency of clopidogrel varies widely between individuals mainly because of cytochrome P450 (CYP) 2C19 genotype variations, which is frequently observed in Asian patients [29, 30]. Resistance to clopidogrel has been reported to potentially result in adverse cardiac events in coronary artery disease [12, 13]. In this study, the difference in PRU value at the follow-up phases tended to be associated with IS-Th after Zilver PTX stent implantation. In the ZEPHYR Registry, interruption of antiplatelet agents was significantly associated with an increased risk of ST [4]. Although the optimal cutoff value of PRU to prevent sustained thrombus attachment after Zilver PTX stent implantation remains to be clarified, we hypothesized that prolonged DAPT or a more potent antiplatelet therapy may be appropriate.

This study has several limitations. First, the results were based on data with a small sample size and the timing of follow-up angioscopy of the patients was based on operators' discretion, thereby posing a risk of patient selection bias. Second, only the segment within the stent implantation where we obtained an adequate image was evaluated in this angioscopic study. Thus, some abnormal angioscopic findings, such as thrombus and yellow plaque, were possibly missed. Third, previous angioscopic observations were limited to coronary artery disease; hence, the clinical implications of abnormal angioscopic findings in PAD have not been elucidated. Finally, the patients were not evaluated by histological analysis or using other imaging modalities, such as intravascular ultrasound or OCT.

Conclusions

Although ongoing healing responses were observed during the first 12 months after implantation, thrombogenic findings following Zilver PTX stent implantation were noted. Considering the delayed vascular healing after Zilver PTX stent implantation, a longer DAPT duration, i.e., over 12 months, could potentially enhance the clinical effectiveness and safety of the stent.

Funding There is no financial support with regard to this manuscript.

Compliance with ethical standards

Conflict of interest Dr. Shinke, Dr. Otake, and Dr. Shite serve as members of the advisory board of Abbott Vascular, Inc. The authors have no conflicts of interest to declare.

Ethical approval A local ethical committee approved this study.

Informed consent All enrolled study patients provided written informed consent to participate in the study.

References

1. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, Machan LS, Snyder SA, O'Leary EE, Ragheb AO, Zeller T (2016) Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. *Circulation* 133:1472–483; discussion 83.
2. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, Zeller T, Roubin GS, Burket MW, Khatib Y, Snyder SA, Ragheb AO, White JK, Machan LS (2011) Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. Circ Cardiovasc Interv 4:495–504
3. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, Snyder SA, O'Leary EE, Tepe G, Scheinert D, Zeller T (2013) Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. J Am Coll Cardiol 61:2417–2427
4. Iida O, Takahara M, Soga Y, Nakano M, Yamauchi Y, Zen K, Kawasaki D, Nanto S, Yokoi H, Uematsu M (2015) 1-year results of the ZEPHYR Registry (Zilver PTX for the femoral artery and proximal popliteal artery): predictors of restenosis. JACC Cardiovasc Interv 8:1105–1112
5. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R (2011) The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol 57:1314–1322
6. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R (2006) Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 48:193–202
7. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R (2007) Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 115:2435–2441
8. Ishihara T, Iida O, Awata M, Nanto K, Nanto S, Uematsu M (2013) Angioscopic assessment of early phase arterial repair after paclitaxel-coated nitinol drug-eluting stent implantation in the superficial femoral artery. Circ J 77:1838–1843
9. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS (2009) Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 360:354–362
10. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, Danchin N, Becquemont L (2009) Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 360:363–375
11. Montalescot G, Sideris G, Meuleman C, Bal-dit-Sollier C, Lellouche N, Steg PG, Slama M, Milleron O, Collet J, Henry P, Beygui F, Drouet L (2006) A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (assessment of the best loading dose of clopidogrel to blunt platelet activation, inflammation and ongoing necrosis) trial. J Am Coll Cardiol 48:931–938
12. Nishio R, Shinke T, Otake H, Sawada T, Haraguchi Y, Shinohara M, Toh R, Ishida T, Nakagawa M, Nagoshi R, Kozuki A, Inoue T, Hariki H, Osue T, Taniguchi Y, Iwasaki M, Hiranuma N, Konishi A, Kinutani H, Shite J, Hirata K (2012) Effect of cytochrome P450 2C19 polymorphism on target lesion outcome after drug-eluting stent implantation in Japanese patients receiving clopidogrel. Circ J 76:2348–2355
13. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, Buonamici P, Gensini GF, Abbate R, Antoniucci D (2011) High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. JAMA 306:1215–1223
14. Sakai S, Mizuno K, Yokoyama S, Tanabe J, Shinada T, Seimiya K, Takano M, Ohba T, Tomimura M, Uemura R, Imaizumi T (2003) Morphologic changes in infarct-related plaque after coronary stent placement: a serial angioscopy study. J Am Coll Cardiol 42:1558–1565
15. Takano M, Mizuno K, Yokoyama S, Seimiya K, Ishibashi F, Okamatsu K, Uemura R (2003) Changes in coronary plaque color and morphology by lipid-lowering therapy with atorvastatin: serial evaluation by coronary angioscopy. J Am Coll Cardiol 42:680–686
16. Kotani J, Awata M, Nanto S, Uematsu M, Oshima F, Hitoshi Minamiguchi, Mintz GS (2006) Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol 47:2108–2111
17. Awata M, Kotani J, Uematsu M, Morozumi T, Watanabe T, Onishi T, Iida O, Sera F, Nanto S, Hori M, Nagata S (2007) Serial angioscopic evidence of incomplete neointimal coverage after sirolimus-eluting stent implantation: comparison with bare-metal stents. Circulation 116:910–916
18. Awata M, Nanto S, Uematsu M, Morozumi T, Watanabe T, Onishi T, Iida O, Sera F, Kotani J, Hori M, Nagata S (2008) Angioscopic comparison of neointimal coverage between zotarolimus- and sirolimus-eluting stents. J Am Coll Cardiol 52:789–790
19. den Heijer P, Foley DP, Hillege HL, Lablanche JM, van Dijk RB, Franzen D, Morice MC, Serra A, de Scheerder IK, Serruys PW (1994) The 'Ermenonville' classification of observations at coronary angioscopy–evaluation of intra- and inter-observer agreement. European Working Group on Coronary Angioscopy. Eur Heart J 15:815–822
20. Ueda Y, Asakura M, Yamaguchi O, Hirayama A, Hori M, Kodama K (2001) The healing process of infarct-related

plaques. Insights from 18 months of serial angioscopic follow-up. J Am Coll Cardiol 38:1916–1922
21. Awata M, Nanto S, Uematsu M, Morozumi T, Watanabe T, Onishi T, Iida O, Sera F, Minamiguchi H, Kotani J, Nagata S (2009) Heterogeneous arterial healing in patients following paclitaxel-eluting stent implantation: comparison with sirolimus-eluting stents. JACC Cardiovasc Interv 2:453–458
22. Ueda Y, Matsuo K, Nishimoto Y, Sugihara R, Hirata A, Nemoto T, Okada M, Murakami A, Kashiwase K, Kodama K (2015) In-stent yellow plaque at 1 year after implantation is associated with future event of very late stent failure: the DESNOTE Study (detect the event of very late stent failure from the drug-eluting stent not well covered by neointima determined by angioscopy). JACC Cardiovasc Interv 8:814–821
23. Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, Lee SW, Kim YH, Whan Lee C, Park SW, Park SJ (2011) Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. Circulation 123:2954–2963
24. Kang SJ, Lee CW, Song H, Ahn JM, Kim WJ, Lee JY, Park DW, Lee SW, Kim YH, Mintz GS, Park SW, Park SJ (2013) OCT analysis in patients with very late stent thrombosis. JACC Cardiovasc Imaging 6:695–703
25. Yokoyama S, Takano M, Yamamoto M, Inami S, Sakai S, Okamatsu K, Okuni S, Seimiya K, Murakami D, Ohba T, Uemura R, Seino Y, Hata N, Mizuno K (2009) Extended follow-up by serial angioscopic observation for bare-metal stents in native coronary arteries: from healing response to atherosclerotic transformation of neointima. Circ Cardiovasc Interv 2:205–212
26. Taniwaki M, Radu MD, Zaugg S, Amabile N, Garcia-Garcia HM, Yamaji K, Jørgensen E, Kelbæk H, Pilgrim T, Caussin C, Zanchin T, Veugeois A, Abildgaard U, Jüni P, Cook S, Koskinas KC, Windecker S, Räber L (2016) Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. Circulation 133:650–660
27. Nikol S, Huehns TY, Hofling B (1996) Molecular biology and post-angioplasty restenosis. Atherosclerosis 123:17–31
28. Schwartz RS (1998) Pathophysiology of restenosis: interaction of thrombosis, hyperplasia, and/or remodeling. Am J Cardiol 81:14e–e17
29. Jinnai T, Horiuchi H, Makiyama T, Tazaki J, Tada T, Akao M, Ono K, Hoshino K, Naruse Y, Takahashi K, Watanabe H, Kita T, Kimura T (2009) Impact of CYP2C19 polymorphisms on the antiplatelet effect of clopidogrel in an actual clinical setting in Japan. Circ J 73:1498–1503
30. Park KW, Kim HS (2012) Options to overcome clopidogrel response variability. Circ J 76:287–292