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PERIPHERAL

1-Year Results of the ZEPHYR Registry (Zilver PTX for the Femoral Artery and Proximal Popliteal Artery)

Predictors of Restenosis

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ABSTRACT

OBJECTIVES This study sought to assess the rate and predictors of 1-year restenosis after drug-eluting stent implantation for femoropopliteal (FP) lesions in patients with peripheral arterial disease.

BACKGROUND Zilver PTX, a paclitaxel-eluting stent for FP lesions, provides superior outcomes to angioplasty and bare-metal stents in clinical trials. However, its real-world outcomes and the associated features remain unclear.

METHODS This was a prospective multicenter study enrolling 831 FP lesions (797 limbs, 690 patients) treated by Zilver PTX implantation. The primary endpoint was 1-year restenosis. Secondary endpoints included major adverse limb event and stent thrombosis.

RESULTS Mean lesion length was 17 ± 10 cm. One-year restenosis, major adverse limb event, and stent thrombosis rates were 37%, 22%, and 2%, respectively. The generalized linear mixed model showed that lesion length ≥16 cm assessed by angiography and distal external elastic membrane area ≤27 mm^2 and minimum stent area ≤12 mm^2 assessed by intravascular ultrasound were independent risk factors for restenosis. One-year restenosis rates were 15% in cases with none of these risk factors and 50% in those with ≥2 risk factors.

CONCLUSIONS The current study demonstrated 1-year real-world outcomes after drug-eluting stent treatment for FP lesions, including challenging ones in clinical practice. Lesion length, external elastic membrane area, and minimum stent area were independent predictors for restenosis. (Zilver PTX for the Femoral Artery and Proximal Popliteal Artery—Prospective Multicenter Registry [ZEPHYR]; UMIN000008433) (J Am Coll Cardiol Intv 2015;8:1105-12)

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DES = drug-eluting stent(s)

DUS = duplex ultrasonography

EEM = external elastic membrane

EVT = endovascular therapy

FP = femoropopliteal

IVUS = intravascular ultrasound

MALE = major adverse limb event

MSA = minimum stent area

ROC = receiver-operating characteristic

ST = stent thrombosis

Zilver PTX (Cook Medical, Bloomington, Indiana) paclitaxel-eluting stent, a recently developed drug-eluting stent (DES), has shown superior long-term outcomes for femoropopliteal (FP) lesions relative to balloon angioplasty and provisional bare-metal stent placement in clinical trials (1,2). However, the population in these trials seems less severe than a real-world population in clinical practice. To date, real-world outcomes of Zilver-PTX implantation for FP lesions including challenging ones remain to be systematically studied. Therefore, we examined the rate and predictors of 1-year restenosis after DES implantation for FP lesions in patients with peripheral arterial disease in clinical settings.

METHODS

The ZEPHYR (Zilver PTX for the Femoral Artery and Proximal Popliteal Artery) registry was a prospective and multicenter study, enrolling patients who had symptomatic peripheral arterial disease due to FP lesions and were treated with Zilver PTX implantation between July 2012 and June 2014. A total of 26 centers participated (Online Appendix). The study was in accordance with the Declaration of Helsinki, was approved by the ethics committee of each participating hospital, and was registered in the University Hospital Medical Information Network Clinical Trial Registry. Written informed consent was obtained from every participant.

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STUDY POPULATION. Patients with symptomatic peripheral artery disease were screened by noninvasive tests to detect limb ischemia and presence of FP lesions. Study enrollment occurred only after satisfying the arteriographic inclusion/exclusion criteria described herein. A total of 831 FP lesions (797 limbs, n = 690) with Zilver PTX implantation were finally enrolled.

ENDOVASCULAR PROCEDURE. The indication for revascularization included symptomatic disease with >50% diameter stenosis determined by angiography and mean pressure gradient >10 mm Hg determined with a 4-F diagnostic catheter. Decision on Zilver PTX implantation was left to the discretion of physicians. For endovascular therapy (EVT), a 6-F sheath was inserted into the femoral artery mostly with a contralateral approach. After 5,000-U heparin infusion, 0.035- or 0.014-inch guidewires were used to cross the lesion. Prior to stent implantation, the guidewire was exchanged for a 0.035-inch one, compatible with the stent delivery system. A final post-dilation was performed for at least 30 s with a noncompliant balloon the size of which was equivalent to distal vessel diameter. Dual antiplatelet therapy with aspirin and either ticlopidine or clopidogrel was recommended to start at least 1 week before and continue for at least 2 months after the stent implantation in accordance with the package insert. Antiplatelet and anticoagulant regimens were used according to the physician's discretion based on patient's condition.

In the current study, intravascular ultrasound (IVUS) was performed to record the data on vessel characteristics immediately after wire crossing and at end of the procedure when possible. IVUS was performed with a commercially available IVUS console and phased-array 20-MHz (Eagle Eye Gold, Volcano Corp., Rancho Cordova, California) or mechanical-scan 40-MHz (OptiCross, Boston Scientific, Marlborough, Massachusetts) IVUS catheters. IVUS was manually pushed forward at a constant speed of 10 mm/s. IVUS and fluoroscopy images were recorded simultaneously to link IVUS images with location using ruler for off-line analysis. External elastic membrane (EEM) area before ballooning and minimal stent area (MSA) (i.e., the smallest cross-sectional area within the stent), after post-dilation were assessed. In occluded cases, IVUS was also used if the wire was in a true lumen or subintimal space. In the current study, IVUS data as well as angiographic data at baseline were evaluated at each participating institute and not by the core laboratory review.

FOLLOW-UP PROTOCOL. All participants were asked to visit centers at 1, 3, 6, and 12 months after EVT. At each visit, ischemic symptoms and ankle-brachial index were evaluated and duplex ultrasonography (DUS) was routinely conducted to evaluate patency. At 12 months after EVT, patients who had not received any reintervention or major amputation were scheduled for readmission at the study institution and underwent follow-up angiography for the treated lesions when possible. The follow-up angiographic data were reviewed at a core laboratory using CAASV software (version 5.7, Pie Medical Imaging, Maastricht, the Netherland). Target lesion revascularization was conducted for ≥50% diameter stenosis within 5 mm of the target lesion after documentation of recurrent clinical symptoms.

ENDPOINTS. The primary endpoint was 12-month restenosis rate assessed by DUS or follow-up angiography, with a tolerance of ±2 months. Restenosis

was defined as recurrence of ≥50% diameter stenosis determined by angiography or a peak systolic velocity ratio >2.4 by DUS (3). Requirement of any reintervention or major amputation (defined as surgical limb excision above the ankle) within 1 year was automatically included in restenosis. Secondary endpoints were major adverse limb event (MALE) and stent thrombosis (ST). MALE was defined as major amputation or any reintervention, including both surgical or endovascular reintervention. ST 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. Data are shown as means ± SD for continuous variables or as percentages for dichotomous variables, unless otherwise mentioned. A p of <0.05 was considered significant. One-year restenosis incidence in the overall population was calculated as $p_{MALE} + (1 - p_{MALE}) \times p_{Restenosis}$, where p_{MALE} and $p_{Restenosis}$ indicate 1-year MALE prevalence in the overall population and 1-year restenosis prevalence in the MALE-free subgroup, respectively. Because cases exist that completed 1-year follow-up without MALE but failed to have patency assessed at 12 ± 2 months, we estimated $p_{Restenosis}$ on the basis of the hypothesis that cases with missing data on patency are subject to the same risk as the remaining observed cases, which is similar to the Kaplan-Meier estimation. Therefore, $p_{Restenosis}$ was calculated to be equal to restenosis prevalence in the population that completed 1-year follow-up without MALE and had patency assessed at 12 ± 2 months. Similarly, p_{MALE} in the overall population (including cases with death or dropout within 1 year) was calculated to be equal to the MALE prevalence in the population that completed 1-year follow-up without death or dropout within 1 year. The 95% confidence interval (CI) of 1-year endpoint incidence rate was estimated by 100,000-time bootstrap resampling. The association of baseline characteristics with restenosis, as well as MALE, was assessed with their odds ratios, which were derived from the generalized linear mixed model with a logit link function. In the model, the interinstitution variability and the intersubject variability were treated as random effects, whereas the following baseline characteristics were treated as fixed effects: critical limb ischemia; restenotic lesion; reference vessel diameter; lesion length; chronic total occlusion; calcification; IVUS-evaluated EEM area; angiography-evaluated post-treatment stenosis; and IVUS-evaluated MSA. An odds ratio of a baseline characteristic without adjustment for other baseline characteristics, named an "unadjusted" odds ratio, was obtained from the mixed model in which the fixed effect was the covariate alone. We conveniently named this model the "univariate" model. On the other hand, an odds ratio of a baseline characteristic with adjustment for other baseline characteristics, named the "adjusted" odds ratio, was obtained from the model whose fixed effects included the covariate of interest plus other covariates. This model was named the "multivariate" model. The predictive ability was assessed by the area under the receiver-operating characteristic (ROC) curve. For its drawing, sensitivity, $p\{X \geq c \mid D = 1\}$, and specificity, $p\{X < c \mid D = 0\}$, were calculated as $p\{X \geq c\} \times p\{D = 1 \mid X \geq c\} / p\{D = 1\}$ and $p\{X < c\} \times p\{D = 0 \mid X < c\} / p\{D = 0\}$, respectively, where X denotes a predictive test of interest, c indicates its cutoff value, and D is a binary indicator of restenosis. $p\{D = 1 \mid X \geq c\}$, $p\{D = 1\}$, $p\{D = 0 \mid X < c\}$, and $p\{D = 0\}$ were estimated as described herein. Monotonicity of the calculated sensitivity and specificity in X was guaranteed by using the nearest neighbor estimation of the bivariate distribution (4). The difference of the area under the ROC curve was tested by 100,000-time bootstrap resampling. Risk stratification analysis was additionally performed according to the number of accumulated risk factors for restenosis. The cumulative incidence of ST was estimated by the Kaplan-Meier method. The association of number of antiplatelet agents (aspirin, thienopyridines, and cilostazol) with ST was evaluated by the Cox regression model with mixed effects. In the model, the interinstitution variability and the intersubject variability were treated as random effects, whereas the number of agents during the follow-up period was entered as a time-dependent covariate with fixed effects. Proportional hazards assumption was made on the basis of the finding that the time-by-covariate interaction term additionally included in the model did not demonstrate statistical significance. Statistical analysis was performed by R (version 3.1.0, R Core Team, Vienna, Austria).

RESULTS

Baseline characteristics of the study population are shown in **Table 1**, indicating their poor comorbidity status. One-third of the population presented critical limb ischemia. Mean lesion length was 17 ± 10 cm; 24% were restenotic lesions, and 15% were in-stent restenosis. A total of 467 limbs (58%) were classified as TASC (Trans-Atlantic Inter-Society Consensus) II class C/D. Perioperative in-hospital complications were observed in 4.9% (34 of 690), including

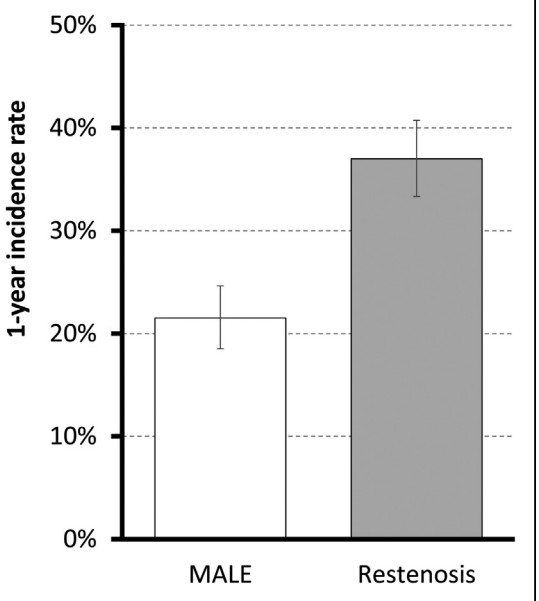
TABLE 1 Baseline Characteristics

Patient characteristics, n = 690	
Age, yrs	73.6 ± 8.8
Male	490 (71)
BMI, kg/m^2	22.1 ± 3.4
Hypertension	585 (85)
Hyperlipidemia	483 (70)
Diabetes mellitus	477 (69)
Renal insufficiency, <30 ml/min/1.73 m^2	258 (37)
Regular hemodialysis	209 (30)
History of smoking, past/current	434 (63)/138 (20)
Cardiovascular disease	347 (50)
Cerebrovascular disease	123 (18)
Number of antiplatelet agents	2.2 ± 0.5
Lower limb characteristics, n = 797	
Critical limb ischemia	255 (32)
Lesion characteristics, n = 831	
Chronic total occlusion	378 (45)
Restenosis	198 (24)
In-stent restenosis	124 (15)
Lesion length, cm	17 ± 10
Distal vessel diameter, mm	5.2 ± 1.0
Percentage of stenosis	90 ± 15
Calcification	541 (65)
No below-the-knee runoff vessel	56 (7)
IVUS-evaluated distal EEM area, mm^2, n = 583	28 ± 10
Percentage of stenosis after stent implantation	4 ± 9
IVUS-evaluated MSA, mm^2, n = 597	15 ± 4

Values are mean ± SD or n (%). Lesion characteristics were assessed by angiography, except for distal EEM area and MSA, which were evaluated by IVUS.

BMI = body mass index; EEM = external elastic membrane; IVUS = intravascular ultrasound; MSA = minimum stent area.

FIGURE 1 1-Year Incidence of Restenosis and MALE



Error bars represent 95% confidence interval. Major adverse limb events (MALE) were automatically included in restenosis for the analysis.

hematoma (n = 16), distal embolism (n = 8), pseudoaneurysm (n = 4), and others (n = 6). Pre- and post-treatment IVUS data were available in 586 lesions (71%) and 632 lesions (76%), respectively.

ONE-YEAR INCIDENCE OF CLINICAL OUTCOMES. Of a total of 690 enrolled patients, 64 patients (9%) died and 44 (6%) dropped out by the end of the study. Of the remaining 697 lesions (84%) in 592 patients (86%), 150 lesions experienced MALE, whereas 547 were free from MALE. Of the 547 MALE-free lesions, 481 lesions had their patency assessed at 12 ± 2 months, whereas 66 did not. Patency was assessed by the core laboratory-reviewed angiography in 208 of the 481 lesions (43%). Figure 1 shows the estimated clinical outcomes at 1 year. One-year incidence of restenosis in the overall population was estimated to be 37% (95% CI: 33 to 41), whereas 1-year MALE was observed in 22% (95% CI: 19 to 25), indicating that MALE accounted for 58% in lesions with restenosis.

PREDICTORS FOR RESTENOSIS. Table 2 shows the logistic regression analysis used to investigate the predictors for 1-year restenosis. When angiographic data were used for analysis, reference vessel diameter (<4.5 cm) and lesion length (≥8 cm) were independent predictors for restenosis, whereas lesion length (≥16 cm), distal EEM area (≤27 mm^2), and MSA (≤12 mm^2) were independent predictors in analysis with angiographic and IVUS data. The use of IVUS data provided a larger area under the ROC curve for predicting restenosis (0.70 vs. 0.65, p = 0.040). In stratification analysis, 1-year restenosis rate was as low as 15% in cases with none of these risk factors, whereas it reached 50% in those with ≥2 risk factors (Figure 2).

We supplementarily analyzed the association of these risk factors with MALE, using the generalized linear mixed model with a logit link function. In the univariate analysis, small reference vessel diameter (<4.5 mm), small distal EEM area (≤27 mm^2), and small MSA (≤12 mm^2), but not the other baseline characteristics, were significantly associated with MALE (all p < 0.05). In the multivariate model in which these 3 variables with significance were entered as fixed effects, only small distal EEM area (≤27 mm^2) had a significant and independent association with MALE; its adjusted odds ratio was 6.09 (95% CI: 2.11 to 17.6).

ST INCIDENCE. Cumulative ST incidence is shown in Figure 3A, revealing its linear increase over time during the 12-month follow-up. The incidence at

TABLE 2 Uni- and Multivariate Analysis for Loss of Patency Assessed With Angiographic and IVUS Data

	Unadjusted Odds Ratio in Univariate Model	Adjusted Odds Ratio in Multivariate Model With Angiographic Data	Adjusted Odds Ratio in Multivariate Model With Angiographic and IVUS Data
Critical limb ischemia	1.03 (0.67–1.59)	0.98 (0.62–1.57)	0.99 (0.54–1.79)
Restenotic lesion			
De novo	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Restenosis after angioplasty	1.35 (0.68–2.69)	1.47 (0.73–2.96)	0.96 (0.35–2.64)
Restenosis after stenting	1.36 (0.80–2.31)	1.23 (0.69–2.20)	1.56 (0.75–3.26)
Angiography-evaluated data			
Reference diameter (distal)			
Q4, ≥6.0 cm	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Q3, 5.1–5.9 cm	1.73 (0.96–3.10)	1.61 (0.87–2.97)	1.64 (0.77–3.51)
Q2, 4.5–5.0 cm	1.22 (0.72–2.09)	1.06 (0.62–1.81)	0.80 (0.40–1.60)
Q1, ≤4.4 cm	2.08 (1.16–3.74)*	1.81 (1.02–3.23)*	1.08 (0.49–2.40)
Lesion length			
Q1, ≤7 cm	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Q2, 8–15 cm	2.18 (1.19–3.98)*	2.10 (1.13–3.88)*	1.71 (0.80–3.64)
Q3, 16–24 cm	3.63 (1.92–6.87)*	3.08 (1.59–6.00)*	3.16 (1.37–7.24)*
Q4, ≥25 cm	3.15 (1.69–5.86)*	2.68 (1.35–5.32)*	2.78 (1.18–6.57)*
Chronic total occlusion	1.75 (1.16–2.62)*	1.27 (0.81–2.00)	0.92 (0.52–1.62)
Calcification	1.18 (0.79–1.77)	1.09 (0.70–1.72)	1.35 (0.77–2.39)
Post-treatment stenosis			
0%	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
0%–25%	0.87 (0.47–1.61)	0.86 (0.50–1.50)	0.87 (0.40–1.91)
<50%	0.70 (0.16–3.05)	0.86 (0.19–3.88)	0.98 (0.16–5.90)
IVUS-evaluated data			
Distal EEM area			
Q4, ≥34 mm^2	1.00 (Ref)	–	1.00 (Ref)
Q3, 28–33 mm^2	1.92 (0.92–3.99)	–	1.72 (0.78–3.80)
Q2, 22–27 mm^2	3.20 (1.56–6.57)*	–	2.34 (1.04–5.25)*
Q1, ≤21 mm^2	6.18 (2.84–13.4)*	–	4.41 (1.84–10.6)*
Post-treatment MSA			
Q4, ≥18 mm^2	1.00 (Ref)	–	1.00 (Ref)
Q3, 15–17 mm^2	1.71 (0.86–3.42)	–	0.99 (0.45–2.19)
Q2, 13–14 mm^2	2.04 (1.00–4.13)*	–	1.07 (0.48–2.41)
Q1, ≤12 mm^2	5.16 (2.44–10.9)*	–	2.38 (1.02–5.51)*

Values are odds ratio for restenosis (95% confidence interval). Dashes indicate that data are not available. *$p < 0.05$.
EEM = external elastic membrane; Ref = reference; other abbreviations as in Table 1.

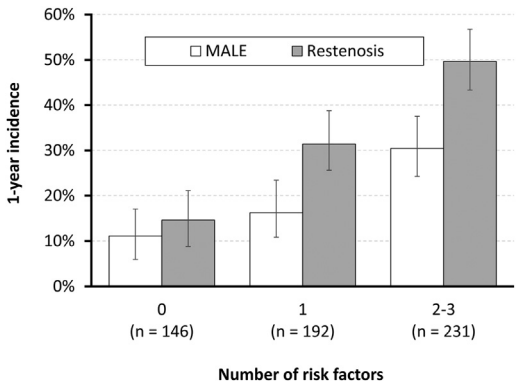
12 months was estimated to be 2%. During the follow-up period, 11 patients interrupted their antiplatelet agents. The reason for the interruption was self-interruption (n = 4); gastrointestinal hemorrhage (n = 2); surgery for renal cancer, major amputation, and peritoneal dialysis catheter (n = 1, respectively); bone fracture due to falling (n = 1); and unspecified (n = 1). The interruption of antiplatelet agents was significantly associated with an increased ST risk (Figure 3B).

DISCUSSION

SUMMARY OF THIS STUDY. The current study demonstrated 1-year real-world outcomes of Zilver PTX treatment for FP lesions including challenging ones seen in clinical practice. The incidence of restenosis varied across lesion characteristics. Lesion length ≥16 cm, distal EEM area ≤27 mm^2, and MSA ≤12 mm^2 were independent risk factors for restenosis. One-year restenosis rate in lesions without these risk factors was 15%, whereas it was 50% in those with ≥2 risk factors. To the best of our knowledge, this is the first study investigating clinical outcomes after Zilver PTX implantation for FP lesions in clinical settings and the associated risk factors including IVUS-evaluated parameters.

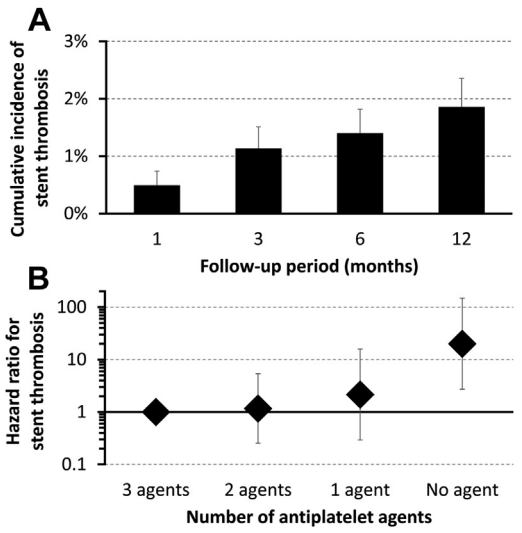
CURRENT STATUS OF ZILVER PTX. Zilver PTX is a recently developed DES for FP lesions. Clinical trials showed that Zilver PTX provides better long-term outcomes than balloon angioplasty and provisional bare-metal stent placement (1,2). However, the population in these trials was limited; FP lesions treated

FIGURE 2 Restenosis and MALE Incidence According to Number or Risk Factors for Restenosis



Risk factors for restenosis were lesion length of ≥16 cm, external elastic membrane area of ≤27 mm^2, and minimum stent area of ≤12 mm^2, which were determined by multivariate analysis using angiographic and intravascular ultrasound parameters (Table 2). Error bars represent 95% confidence interval. MALE = major adverse limb events.

FIGURE 3 Cumulative ST Incidence



(A) The cumulative stent thrombosis (ST) incidence rate in cases keeping antiplatelet therapy during the follow-up period (n = 820) and its standard error are shown. The incidence was estimated by the Kaplan-Meier method after excluding cases with antiplatelet therapy interrupted during the study period (n = 11), the corresponding incidence at 1 year was 15 ± 10%. Note that the cumulative incidence of which was increased linearly even when the subjects were limited to those keeping antiplatelet therapy. **(B)** The hazard ratio of number of antiplatelet agents for ST and the 95% confidence interval, which were estimated in the Cox model in which the number of antiplatelet agents was treated as a time-dependent covariate, are shown.

in clinical settings are more varied than those in the trials. Real-world clinical outcomes of DES implantation for FP lesions remained unrevealed. Previous studies on catheter treatment including coronary and peripheral interventions indicate that durability of vessel after catheter treatment are largely influenced by lesion characteristics such as: 1) vessel diameter and morphology (easy to dilate or not) (5,6); 2) lesion type (new or not) (7); and 3) lesion length (short or long) (8). However, to date, little is known about the association of these lesion characteristics with clinical outcomes after DES implantation for FP lesions.

FINDINGS AND INTERPRETATIONS. In the current study, 1-year restenosis rate in the overall population was 37%, which was apparently worse than that reported in previous Zilver PTX trials. This discrepancy might come from the severity of the current study population's conditions. The current study included more complex lesions, reflecting the real-world settings, which might lower the patency rate. Indeed, we revealed that the restenosis risk varied across lesion characteristics and that the subgroup without complexity had a low restenosis risk, which were comparable to that reported in previous trials. Another possible explanation for the discrepancy in the reported restenosis rate might be the statistical methodology for its evaluation. Previous studies adopted the Kaplan-Meier method for their patency analysis. However, this method is originally for right-censored data and is not suitable for the analysis including left-censored data such as restenosis. This misapplication of the Kaplan-Meier method might underestimate the restenosis rate in previous reports.

The risk analysis revealed that lesion length was independently associated with future restenosis, with the threshold of ≥16 cm. Given that lesion length of ≥25 cm had a similar restenosis risk to that of 16 to ~24 cm, the restenosis risk might not increase linearly in Zilver PTX implantation for FP lesions. Supplementary analysis showed that long lesion length was not significantly associated with future risk of MALE. However, the number of events observed was smaller than for restenosis, and therefore a smaller statistical power might cause the current nonsignificant association. Future studies that have a larger sample size and that can observe more MALE events will be needed to conclude that lesion length is not associated with MALE risk at all.

Distal EEM area was another independent predictor for restenosis. The finding indicates that a smaller vessel would be subject to a poorer stent patency. Similarly, in analysis without IVUS data, a smaller angiography-evaluated reference vessel diameter was significantly associated with a higher risk of restenosis. However, the variable lost its statistical significance after adjustment for IVUS parameters, suggesting that the evaluation by IVUS would provide more reliable information.

The other risk factor for restenosis was a smaller MSA, indicating that lesions difficult to dilate would be subject to a high restenosis risk. To date, no reliable data were available regarding an optimal stent expansion in FP lesions. The current finding suggests that an implanted Zilver PTX with MSA $\leq$12 mm^2 has a high risk of restenosis. Future studies will be needed to validate the usefulness of this cutoff point.

Interestingly, restenotic lesions, including in-stent stenotic lesions, were not associated with any elevated risk for loss of patency after DES implantation. From latest experience and evidence in FP EVT, non-de novo FP lesions are described as a critical risk factor for refractory restenosis (7). The current finding was in contrast to these previous experiences, implying that the Zilver PTX might resolve this critical issue of rerestenosis.

The current study demonstrated that the predictive ability for restenosis, assessed by the area under the ROC curve, was statistically improved when IVUS data were used in addition to angiographic data. It is possible that IVUS provides more detailed and precise information on pre- and post-treatment vessel characteristics than angiography does. The current findings suggest that IVUS offers some help in predicting future risk of restenosis after DES implantation. However, the predictive ability did not seem to reach the level that was previously reported in coronary intervention (9,10). There remains room to improve the predictive ability for restenosis in FP intervention.

The 1-year ST incidence was 2%. It is of clinical note that the cumulative ST incidence rate did not reach the plateau but was linearly increased even after 3 months. Identification of its risk factors is needed. In addition, the current study, conducted in clinical settings, included a few patients interrupting antiplatelet therapy after DES implantation and observed that the interruption markedly increased the ST risk. The importance of continuing antiplatelet therapy was reconfirmed.

STUDY LIMITATIONS. First, the current study included only Japanese patients, and results should be confirmed in other ethnic groups. Second, this study was not designed to compare the durability of Zilver PTX implantation with other treatments. It remains to be studied whether Zilver PTX implantation is superior to other treatments in real-world settings. Third, IVUS was not performed for all cases. In addition, it was manually used for lesion assessment. However, we believe that little heterogeneity existed in usage and evaluation of IVUS, based on a common agreement in clinical practice of coronary intervention.

Fourth, the IVUS assessment in initial treatment and the DUS assessment for restenosis were not conducted under core laboratory review, simply because we could not raise enough research funds to conduct them. Although this might undermine the reliability of restenosis assessment, each participating site has clinical experience conducting pivotal trials on nitinol stents for FP lesions. We believe that these accumulated experiences minimized the variability. Fifth, the times to restenosis or ST were not exactly assessed because of variable time intervals between symptom onset and assessment. Sixth, the current study enrolled the lesions in which the DES was successfully deployed; therefore, we were unable to collect the data regarding the success rate.

CONCLUSIONS

We demonstrated real-world 1-year outcomes after Zilver PTX implantation for FP lesions, including challenging cases. Lesion length, EEM area, and MSA were independent predictors for restenosis.

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PERSPECTIVES

WHAT IS KNOWN? Zilver PTX has not totally relieved restenotic risk after EVT for FP lesions.

WHAT IS NEW? Restenosis occurs at a certain frequency in clinical practice.

WHAT IS NEXT? IVUS evaluation gives additive information for predicting 1-year restenotic risk after Zilver PTX implantation.

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KEY WORDS drug-eluting stent, endovascular therapy, femoropopliteal lesion, intravascular ultrasound, restenosis

APPENDIX For a list of participating centers, please see the online version of this paper.