The Characteristics of In-Stent Restenosis After Drug-Eluting Stent Implantation in Femoropopliteal Lesions and 1-Year Prognosis After Repeat Endovascular Therapy for These Lesions

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ABSTRACT

OBJECTIVES This study sought to investigate the characteristics of in-stent restenosis (ISR) after drug-eluting stent (DES) implantation for femoropopliteal (FP) lesions, and to examine 1-year prognosis after repeat endovascular therapy (re-EVT) for these DES-ISR.

BACKGROUND The morphology of DES-ISR and its association with clinical outcomes after re-EVT have not been well examined.

METHODS This was a subanalysis of the ZEPHYR (Zilver PTX for the femoral artery and proximal popliteal artery) study. The current study included 210 cases with loss of patency confirmed 1 year after DES implantation. Morphology of DES-ISR was classified into the following subgroups: class I, focal lesions (<50 mm in length), class II, diffuse lesions (>50 mm in length), and class III, totally occluded ISR. One-year prognosis after re-EVT for DES-ISR was assessed by restenosis and major adverse limb events (MALE).

RESULTS Classes I, II, and III accounted for 50%, 25%, and 25% of DES-ISR, respectively. Factors associated with the morphology of DES-ISR were the presence of chronic total occlusion and the size of the external elastic membrane area before DES implantation (p = 0.009 and 0.017). Compared with the class I restenotic lesion, the class II and III lesions had a significantly higher risk of restenosis (74% and 78% vs. 53%; p = 0.048 and 0.019, respectively) and MALE (56% and 56% versus 32%; p = 0.025 and 0.022, respectively) 1 year after re-EVT.

CONCLUSIONS We evaluated the characteristics of ISR after DES implantation for FP lesions and 1-year prognosis of re-EVT for DES-ISR. The morphology of DES-ISR had a significant association with 1-year prognosis after re-EVT. (J Am Coll Cardiol Intv 2016;9:828–34) © 2016 by the American College of Cardiology Foundation.
Clinical outcomes of endovascular therapy (EVT) for femoropopliteal (FP) lesions have improved recently thanks to the development of current devices including new-generation bare-metal nitinol stents (BNS) and drug-eluting stents (DES). However, a substantial incidence of in-stent restenosis (ISR), which is continuously increasing during the chronic phase, is reluctantly found in clinical setting (1-6).

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The morphology of post-BNS restenosis is a clinically important determinant in predicting the future occurrence of recurrent ISR after balloon angioplasty and was classified into the following 3 subgroups: class I, focal lesions (<50 mm in length), class II, diffuse lesions (>50 mm in length), and class III, totally occluded ISR (7,8). Particularly, the prognosis of balloon angioplasty after post-BNS class III restenosis is direly poor, and the rates of repeat reintervention and conversion to bypass surgery are consequently high. However, there are no reports on the morphology of ISR after DES implantation. The aim of the current study was to investigate the characteristics of ISR after DES implantation for FP lesions, and to examine 1-year prognosis after repeated endovascular therapy (re-EVT) for these DES-ISR lesions.

METHODS

STUDY POPULATION AND DEFINITIONS. This was a subanalysis of the ZEPHYR (Zilver PTX for the Femoral Artery and Proximal Popliteal Artery) study. The ZEPHYR study was a prospective multicenter study enrolling patients with femoropopliteal lesions undergoing Zilver PTX implantation between July 2012 and April 2013. The details of the study protocol and the 1-year results were described elsewhere (9). The study was in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating hospital. Written informed consent was obtained from every participant. Antiplatelet regimens during the follow-up period were used at the physician’s discretion on the basis of patient’s condition.

In the ZEPHYR study, external elastic membrane (EEM) area, defined as the area enclosed by the media to adventitia interface, and minimal stent area (MSA), defined as the smallest stent area within the implanted stent, were evaluated by intravascular ultrasound (IVUS).

The current study analyzed a total of 210 cases, whose ISR was confirmed at 1 year after DES implantation. The distribution of the subsample among the centers in the ZEPHYR study are shown in Online Figure A. DES-ISR was evaluated using follow-up angiography or duplex ultrasonography (DUS), and was categorized into class I, II, and III, similarly to BNS-ISR in Figure 1 (7,8). In brief, focal non-occlusive lesions (≤50 mm in length) were categorized as class I, whereas diffuse non-occlusive ones (>50 mm in length) were categorized as class II. Class III was defined as totally occluded lesions. Cases with stent thrombosis were excluded.

Of the 210 cases with DES-ISR, 134 cases (64%) underwent re-EVT to re-recanalize the restenotic lesions. One-year prognosis after the re-EVT was evaluated with restenosis (i.e., recurrence of in-stent stenosis) and major adverse limb events (MALE). One-year restenosis after re-EVT was again assessed by follow-up angiography or DUS, 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 (10). Requirement of any reintervention (either endovascular or surgical) or major amputation (defined as surgical limb excision above the ankle) within 1 year was automatically included in the outcome. MALE was defined as any reintervention or major amputation.

STATISTICAL ANALYSIS. Data are shown as the mean ± SD for continuous variables or as percentages for dichotomous variables, unless otherwise noted. A p value <0.05 was considered as statistically significant. p Values for trend regarding baseline characteristics at DES implantation were obtained from the 1-way analysis of variance for continuous variables, and from the linear-by-linear association test for discrete variables. The difference in treatment strategy among subgroups was tested by the chi-square test. One-year incidence rate of restenosis (i.e., recurrence of in-stent...
stenosis) was calculated as: \( P_{\text{MALE}} + (1 - P_{\text{MALE}}) \times P_{\text{Restenosis}} \), in accordance with the previous report (9), where \( P_{\text{MALE}} \) and \( P_{\text{Restenosis}} \) indicate 1-year MALE prevalence in the overall population of interest and 1-year restenosis prevalence in the MALE-free subgroup, respectively. The 95% confidence interval (CI) and intergroup difference of the incidence rates were estimated by 10,000-time bootstrap resampling. The bootstrap resampling was performed by R version 3.1.0 (R Development Core Team, Vienna, Austria), whereas the other statistical analyses were by IBM SPSS Statistics version 22 (SPSS, Chicago, Illinois).

RESULTS

Table 1 shows the baseline characteristics at DES implantation of the study population. The mean age of the study population was 73 ± 9 years, and 67% (141 of 210) were male. The prevalence of critical limb ischemia was 25% (n = 58), and average lesion length was 18 ± 9 cm. IVUS-evaluated EEM area and MSA were 25 ± 9 mm\(^2\) and 14 ± 4 mm\(^2\), respectively. In the 210 cases with loss of patency 1 year after DES implantation, the proportion of classes I, II, and III

| TABLE 1 Baseline Characteristics at DES Implantation of Study Population (N = 210) |
|-----------------------------|-----------------------------|
| Age, yrs                    | 73 ± 9                      |
| Male                        | 141 (67)                    |
| Diabetes mellitus           | 149 (71)                    |
| Regular dialysis            | 64 (30)                     |
| Smoking                     | 51 (24)                     |
| Critical limb ischemia      | 53 (25)                     |
| Prior history of EVT        | 61 (29)                     |
| Calcification               | 132 (63)                    |
| Chronic total occlusion     | 107 (51)                    |
| Lesion length, cm           | 18 ± 9                      |
| IVUS-evaluated EEM area, mm\(^2\), n = 447 | 25 ± 9                      |
| IVUS-evaluated MSA, mm\(^2\), n = 458 | 14 ± 4                      |

Values are mean ± SD or n (%).

DES = drug-eluting stent; EEM = external elastic membrane; EVT = endovascular therapy; IVUS = intravascular ultrasonography; MSA = minimal stent area.
was 50% (n = 106), 25% (n = 52), and 25% (n = 52), respectively (Figure 2). The comparison in background characteristics at DES implantation among the restenotic classes are shown in Table 2. This univariate analysis showed that chronic total occlusion (CTO) and IVUS-evaluated EEM area were significantly associated with the morphology of DES-ISR. We subsequently tried multivariate analysis (Table 3), indicating that CTO and EEM area, but not diabetes mellitus (DM), were independently associated with DES-ISR classes.

As shown in Table 4, the treatment strategy for DES-ISR were not significantly different among the DES-ISR classes; approximately two-thirds underwent re-EVT.

Figure 3 shows 1-year restenosis rate after re-EVT for loss of patency. One-year incidence of restenosis in classes I, II, and III was estimated to be 53% (95% CI: 39 to 67%), 74% (58 to 90%), and 78% (16 to 94%), whereas 1-year MALE was observed in 32% (20 to 45%), 56% (39 to 73%), and 56% (41 to 72%), respectively. Compared with the class I restenotic lesions, class II and III lesions had a significantly higher risk of restenosis (p = 0.048 and 0.019, respectively) and MALE (p = 0.025 and 0.022, respectively). We subsequently tried multivariate analysis. We performed the logistic mixed model whose dependent variable was restenosis after re-EVT for DES-ISR. In the model, ISR morphology (class II vs. class I), CTO, and EEM area were treated as fixed effects, whereas intersubject variability was treated as random effects. Consequently, the adjusted odds ratios of ISR class II versus class I, CTO, EEM area were 2.98 (95% CI: 1.00 to 8.87) (p = 0.049), 1.29 (95% CI: 0.47 to 3.50) (p = 0.621), and 1.29 (95% CI: 0.75 to 2.24) (p = 0.188).

A comparison of 1-year restenosis rate after re-EVT for DES-ISR is shown in the table.
(p = 0.357) per 10-mm² increase, respectively, indicating that ISR morphology, but not CTO or EEM area, had an independent association with restenosis risk after re-EVT.

**DISCUSSION**

**SUMMARY OF THIS STUDY.** The current study was designed to investigate the characteristics of ISR after DES implantation for FP lesions, and to examine 1-year prognosis after re-EVT for these DES-ISR lesions. We demonstrated that: 1) class I (i.e., focal) accounted for one-half of DES-ISR cases, whereas the other one-half was evenly divided between class II (i.e., diffuse) and class III (i.e., totally occluded) ISR; 2) lesions with CTO and smaller EEM area at DES implantation were significantly associated with the restenotic pattern 1 year after DES implantation; 3) 1-year restenosis rate after re-EVT for DES-ISR was suboptimal, and especially class II and III had an extremely dire prognosis. Supplementary multivariate analysis for a minimal adjustment suggests that CTO and EEM area, but not DM, were independently associated with ISR morphology and that ISR morphology was associated with post-re-EVT restenosis risk independently of CTO and EEM area. However, because the current sample size was small, the current findings regarding these independent associations may be inconclusive. Future studies with a larger sample size are needed to confirm these findings.

**INTERPRETATIONS OF THE CURRENT FINDINGS.**

Zilver PTX is the only available drug-eluting stent for treating peripheral artery disease patients presenting FP lesions. Recent reports indicate that long-term results of Zilver PTX are superior to those of BNS and balloon angioplasty (2). However, the consequence of DES-ISR after re-EVT has not been well examined. In the BNS era, classification and clinical impact of the ISR pattern has been reported; balloon angioplasty for the BNS-ISR including classes I and II is feasible, whereas the risk of recurrent ISR and occlusion after balloon angioplasty is remarkably high for ISR class III. The current study suggested that the ISR pattern after DES implantation is somewhat different from that of BNS. Although the ZEPHYR study frequently enrolled complicated lesions, class II and III lesions in total accounted for only one-half of the cases. This was in contrast to BNS-ISR, where class II and III lesions were more familiar and found in about two-thirds. We speculated that the effectiveness of the drug-eluting system itself is related to suppression of diffuse neointimal hyperplasia, which would decrease the frequency of class II and III ISR compared with BNS. Predominance of the class I pattern in DES-ISR would possibly be a clinically favorable feature, because class I lesions are generally regarded as easy to recanalize by re-EVT. This difference of the ISR-pattern distribution between DES and BNS might lead to a possible superiority of DES to BNS. However, because the current study did not directly compared DES to BNS, it remains unrevealed whether DES would be superior to BNS in subsequent treatment for ISR. Future studies are needed to confirm this point. Although class I lesions had a lower risk of restenosis and MALE after re-EVT compared with class II and III lesions in the current

### TABLE 4 1-Year Stenotic Status and Treatment Strategy

<table>
<thead>
<tr>
<th>Class</th>
<th>(Focal)</th>
<th>(n = 106)</th>
<th>(Diffuse)</th>
<th>(n = 52)</th>
<th>(Occlusive)</th>
<th>(n = 52)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>39 (37)</td>
<td>14 (27)</td>
<td>18 (35)</td>
<td></td>
<td></td>
<td></td>
<td>0.454</td>
</tr>
<tr>
<td>Re-EVT</td>
<td>65 (61)</td>
<td>37 (71)</td>
<td>32 (62)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bypass conversion</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major amputation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%).

Re-EVT = repeat endovascular therapy.

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Error bars indicate 95% CI. One-year incidence of restenosis in classes I, II, and III was estimated to be 53% (95% CI: 39% to 67%), 74% (58% to 90%), and 78% (16% to 94%), whereas 1-year MALE was observed in 32% (20% to 45%), 56% (39% to 73%), and 56% (41% to 72%), respectively. Asterisks demonstrate p < 0.05 versus cases undergoing re-EVT for class I restenosis. Class I, focal nonocclusive lesion (<5 cm in length); class II, diffuse non-occlusive lesion (<5 cm in length); class III, occlusive lesion. CI = confidence interval; MALE = major adverse limb events; re-EVT = repeat endovascular therapy; other abbreviations as in Figures 1 and 2.
study population, the absolute incidence rates of them were not low at all. These high rates may come from the fact that the target lesions were so complicated in the current study. Further investigation will be needed to identify the population with a low risk of re-restenosis after re-EVT for DES-ISR and to reveal the real indication of DES use in clinical setting. Additionally, some ingenuities, including use of drug-eluting balloons, would be needed for improvement of re-EVT results.

In terms of the morphology of DES-ISR, CTO and IVUS-evaluated EEM area were significantly associated with DES-ISR patterns, demonstrating that the presence of CTO and lesions in smaller vessels are risk factors for future occurrence of the severe DES-ISR pattern. Although vessel size cannot be modified by endovascular approaches, CTO lesions can be modified by endovascular approaches. Additional approaches, including plaque modification by using some atherectomy devices before DES implantation, would potentially decrease the risk for occurrence of the severe DES-ISR pattern, compared with simple DES implantation.

The current study also demonstrated the tendency toward negative association between DM and severe DES-ISR pattern, although the association was not statistically significant. It remains unclear what this tendency implies. Future studies will be needed to confirm this apparent association.

**CLINICAL IMPLICATION.** To the best of our knowledge, this is the first study evaluating the characteristics of DES-ISR, and 1-year results after re-EVT for these lesions. In the current situation, DES is reliable and promising devices in reducing the restenosis rate for FP lesions, and will be more frequently used in the clinical setting. Consequently, it is speculated that the number of DES-ISR simultaneously will increase with its use. Therefore, our finding will be clinically meaningful and helpful in considering the indication for endovascular revascularization, because it may inform the decision-making process for FP revascularization.

**STUDY LIMITATIONS.** First, in the current study, the assessment for recurrent DES-ISR was not conducted under core laboratory review, simply because of insufficient research funds for conducting it. As mentioned in initial report of the ZEPHYR study, each participating site has clinical experience conducting pivotal trials on nitinol stents for FP lesions. We believe that these accumulated experiences minimized the variability. Second, the number of DES-ISR might be relatively small. However, the number was similar to that of recent studies on BNS-ISR, indicating the current study would have a similar statistical power compared with them. Third, we only assessed 1-year prognosis after re-EVT for DES-ISR. Further investigation of long-term follow-up will be needed to assess the consequence of re-EVT for DES-ISR.

**CONCLUSIONS**

We evaluated the characteristics of ISR after DES implantation for FP lesions and 1-year prognosis after re-EVT for DES-ISR. Characteristics including CTO and EEM area at DES implantation were significantly associated with restenotic status 1 year after DES implantation. One-year prognosis after re-EVT for DES-ISR lesions was suboptimal.

**REFERENCES**


KEY WORDS drug-eluting stent(s), femoropopliteal lesion, in-stent restenosis

APPENDIX For a list of the participating centers and investigators, and a supplemental figure, please see the online version of this article.