Usage of Contemporary Drug-Eluting Stent by Japanese Interventional Radiologists for Femoropopliteal In-Stent Restenosis lesions -COMBAT-ISR study-

K. Takayama*, S. Ichihashi**, K. Kichikawa**, for the COMBAT-ISR investigators
*Department of Radiology and Interventional Neuroradiology, Ishinkai Yao General Hospital, Yao, Japan
**Department of Radiology, Nara Medical University, Kashihara, Japan

Background

In-Stent Restenosis (ISR) after femoropopliteal (FP) interventions is an increasing problem. Because rate of recurrent ISR was high. In particular when stent occlusion occurred, the rate of re-ISR was 83.3% (1). There are some solutions including drug stent technology to avoid re-ISR. There were already some reports to prevent re-ISR using drug eluting stent (ZILVER-PTX) (2). In addition, it has been recently reported that new Drug-Eluting Stent (Eluvia stent) was better than ZILVER-PTX for FP disease (3). This new Drug-Eluting Stent has also been expected to avoid re-ISR. In February 2019, Eluvia stent became available in Japan. Therefore no published studies have examined Eluvia Drug-Eluting Stent in the treatment of FP ISR in Japanese population.

Objective

This study will seek to evaluate the outcomes of Eluvia stent treatment for femoropopliteal ISR.

Materials & Methods

A prospective study was conducted at least 17 medical centers in Japan (Table 1). COMBAT-ISR study had been enrolled from March 2019 to December 2019 with a target number of 100 patients. COMBAT-ISR study included patients who had Symptomatic ISR in the femoropopliteal artery. Inclusion/Exclusion Criteria was shown in Table 2.

IVR procedure
Patients were treated with the ELUVIA drug eluting vascular stent (Boston Scientific, Marlborough, MA, USA, Indiana) The protocol specified planned treatment with a maximum of 3 ELUVIA drug eluting vascular stents per patient (maximum length 360mm). Pre and post dilation were performed at the interventionalist discretion.
Unfractionated heparin was administered during the procedure to maintain an activated clotting time over 250 second. Dual antiplatelet agent (Aspirin 81 to 100 mg and Clopidogrel 75 mg) was administered at least 24 h before the procedure. Following treatment, Dual antiplatelet therapy was continued for 90 days and mono antiplatelet therapy was continued indefinitely.

Endpoints
The primary endpoint is primary patency at 6, 12-month follow-up. Secondary endpoints are technical success rate, and the occurrence of major adverse events, defined as stent thrombosis and all causes of death through 1 month, major amputation of the target limb through 12 months, or target lesion revascularisation through 12 months. Primary vessel patency was defined as duplex ultrasound peak systolic velocity ratio ≦ 2.4, without clinically driven target lesion revascularization (TLR) or bypass of the target lesion.

Results

Thirty-two patients were enrolled from February 2019 to December 2019 (Table 2). We didn't reach the target number, therefore the enrollment will be extend by March 2020. Full baseline and procedural characteristics are summarized in Table 3. Technical success was 100% (36 of 36) of ISR lesions. Stent thrombosis occurred in one patient (2.8%) at 2 weeks postoperative days. This case seemed to be associated with clopidogrel resistance. Because VerifyNow showed PRU (P2Y12 reaction units) was 235 on emergency re-admission. No death occurred in any patients.
At 6 months, the primary patency rate was 95.6% (23/24). The Kaplan-Meier estimate of primary patency was 94.4% at 6 months (Figure 1).

Center	Principle Investigator	The number of Enrollment
Ishinkai Yao General Hospital, Yao, Japan	Katsutoshi Takayama MD	23
Nara Medical University, Kashihara City, Japan	Shigeo Ichihashi, MD Kimihiko Kichikawa, MD	11
Matsue Seikyo General Hospital,Matuse, Japan	Tomonori Nakamura, MD	1
Mito Saiseikai General Hospital, Mito, Japan	Yoshiro Chiba MD	1
Kobe University Hospital, Kobe, Japan	Kouji Sugimoto MD	0
Tottori University, Faculty of Medicine, Yonago, Japan	Masayuki Endo MD	0
Tokai University Hachioji Hospital, Hachioji, Tokyo, Japan	Merumitus Hasebe, MD	0
Hyogo Brain and Heart Center at Himeji, Himeji, Japan	Ryuta Kawasaki, MD	0
Keio University School of Medicine, Tokyo, Japan	Masanori Inoue MD	0
Wakayama Medical University , Wakayama, Japan	Motoki Nakai, MD	0
Nippon Medical School Musashi Kosugi Hospital, Kanagawa, Japan	Hiroshi Kawamata, MD Hiroshi Tajima,MD	0
Tsuchiya General Hospital, Hiroshima, Japan	Tomoyasu Sato MD	0
Oita University Faculty of Medicine, Oita, Japan	Morio Hongo, MD	0
Asahikawa City Hospital, Hokkaido, Japan	Makoto Hanawa, M.D	0
Iwate Medical College, Morioka, Japan	Ryoichi Tanaka, M.D	0
Nippon Medical School Hokuso Hospital, Chiba, Japan	Takahiko Mine, MD	0
Sumitomo Hospital, Osaka City, Japan	Kouji Yamamoto MD	0
Total		36

Table 1. Medical Centers and Investigators of COMBAT-ISR study

Major inclusion criteria
1) Age > 40 years
2) Symptomatic ISR (Rutherford-Becker category 2 to 5), ISR >50% in the SFA and P1 segment of the popliteal artery, and a distal runoff of at least 1 artery
Major Exclusion criteria
1) Inability to give written informed consent;
2) Known allergy, hypersensitivity, or intolerance to radiologic contrast media, aspirin, clopidogrel and Paclitaxel
3) Creatinine >2.5 mg/dl (except hemodialysis patients)

Table 2. Major inclusion criteria and exclusion criteria of COMBAT-ISR study

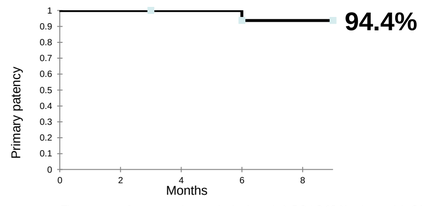
During followed-up, the MAE rate was 5.6% (2/36). MAEs were observed in one patient. This patient who stent thrombosis occurred in and underwent TLR. No death and target limb amputations occurred.

Discussion

Zeller et al. (2) reported 108 patients and 119 lesion who were enrolled in the ZILVER-PTX single-arm study which is Paclitaxel-coated stent. The mean lesion length was 13.3 cm. Primary patency was 78.8% at 1 year. Primary patency in this study was better than conventional POBA (1).
On the other hand, Gray et al. (3) has reported 465 patients who were randomly assigned to Eluvia (n=309) or to Zilver PTX (n=156). The mean lesion length was 8.65 cm. Primary patency at 1 year was significantly higher in the Eluvia group (86·8%) than in the Zilver PTX group (81·5%). Therefore the present study regarding ISR also is expected to show that the primary patency is better in Eluvia than in Zilver PTX.
However there is one biggest concern about Eluvia stent. Katsanos et al. reported that there is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs (4). Eluvia was not included in these meta-analyses. Plus, there were quite different regarding the total volume of the drug and the duration of the drug release between these stents. Therefore Eluvia stent will be expected not to be associated with increased risk of death, because there was no evidence to prove increased risk of death following application of paclitaxel-coated stents in coronary field. That is why the total volume of drug and the duration of the drug release may be associated with increased risk of death following application of paclitaxel-coated balloon and stents.

	N=34, 36 limbs
Male, n (%)	22 (61.1%)
Mean age ± SD	73.7 ± 9.4
Hypertension, n (%)	29 (80.6%)
Diabetes, n (%)	24 (66.7%)
Hyperlipidemia, n (%)	24 (66.7%)
Previous smoking, n (%)	18 (60.0%)
Active smoking, n (%)	5 (13.3%)
Coronary artery disease, n (%)	7 (19.4%)
Cerebrovascular disease, n (%)	9 (25.0%)
Rutherford stage II-III n (%)	28 (77.8%)
Rutherford stage VI, n (%)	4 (11.1%)
Rutherford stage V, n (%)	4 (11.1%)
Lesion	
In-stent stenosis	24 (66.7%)
In-stent occlusion	12 (33.3%)
Length of the treated lesion mean ± SD (cm)	20.3 ± 8.6
The number of distal run off	
1	22 (61.1%)
2	10 (27.8%)
3	4 (11.1%)
Pre-operative ankle-brachial index	0.49 ± 0.33

Table 3 Demographics and baseline characteristics



The average of postoperative monitoring(months): 5.9±2.18 Numbar at risk: 24

Figure 1. Kaplan-Meier Estimates of Primary Patency at 6 months

Conclusion

Treatment of femoropopliteal ISR with Eluvia stent was expected to result in favorable acute and midterm outcomes.

References

(1) Tosaka A et al. Classification and clinical impact of restenosis after femoropopliteal stenting. J Am Coll Cardiol 2012;59:16–23.
(2) Zeller T et al. Treatment of femoropopliteal in-stent restenosis with paclitaxel-eluting stents. J Am Coll Cardiol Intv 2013;6:274–81.
(3) Gary et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-I nferiority trial.
(4) Katsanos et al . Risk of Death Following Application of Paclitaxel-Coated Balloons andStents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled TrialsJ Am Heart Assoc. 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.)