Comparing the 1-year clinical outcomes of polymer-based paclitaxel-eluting stent implantation between hemodialysis and non-hemodialysis patients: A prospective, observational, single-center study".

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Research Article

Keywords: endovascular therapy, femoropopliteal artery disease, hemodialysis, implantation, paclitaxel, patency, polymer-based paclitaxel-eluting stent, revascularization

Posted Date: February 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1315309/v1

Abstract

Background: Previous studies have shown favorable clinical outcomes of polymer-based paclitaxel-eluting stents (PB-PESs) in patients with femoropopliteal artery (FPA) disease. However, the effectiveness of PB-PES in hemodialysis (HD) patients has not been reported. The aim of this study was to compare the clinical performance of PB-PESs between HD and non-HD patients with symptomatic FPA disease.

Materials and Methods: Between January 2019 and February 2020, 52 consecutive patients (mean age: 75.5 years; 42 men) underwent PB-PES implantation for symptomatic FPA diseases. Of these, 29 patients received HD and were classified into the HD cohort. The remaining 23 patients were classified into the non-HD cohort. Clinical outcomes were compared between the two cohorts. The primary efficacy endpoint was the primary patency at 12 months, and the primary safety endpoint was the 12-month incidence of major adverse cardiovascular and limb events (MACLEs), which were defined as the composite of the incidence of all-cause death, major amputation, stent thrombosis, and clinically driven target lesion revascularization (CD-TLR).

Results: The overall primary patency rate was 93.3%. No significant difference existed in primary patency between the HD and non-HD cohorts (91.7% vs. 95.0%, *P*=0.577). The overall incidence rate of MACLEs was 16.6%, and the incidence rate was not significantly different between the HD and non-HD cohorts (20.2% vs. 13.3%, *P*=0.954). The incidence of stent thrombosis was not different between the HD and non-HD cohorts (8.3% vs. 5.0%, *P*=0.956).

Conclusion: PB-PESs have exceptional 1-year primary patency and acceptable safety in HD patients and non-HD patients.

Level of Evidence: Level 3, nonrandomized, follow-up study

Background

The development of dedicated devices and growing evidence have increased the adoption of endovascular therapy (EVT) as a revascularization strategy for treating femoropopliteal artery (FPA) disease [1]. The most recent guidelines strongly support the use of the polymer-free paclitaxel-eluting stent (PF-PES) for treating FPA lesions [2]. The Zilver PTX (Cook Medical, LLC, Bloomington, IN, USA), a PF-PES, demonstrated a 5-year clinical benefit over standard treatment [3]. However, a PB-PES, the Eluvia fluoropolymer-based paclitaxel-eluting stent (Boston Scientific Corp., Maple Grove MN, USA) exhibited a more favorable 12-month durability than did the PF-PES in a randomized control trial [4]. Real-world data on PB-PES also report a favorable (87–91%) 1-year primary patency [5, 6].

EVT may not achieve sufficient long-term results in hemodialysis (HD) patients, owing to the presence of calcification, occlusion, and poor outflow [7]. PB-PES implantation is expected to improve the outcomes in HD patients; however, the effectiveness of PB-PES in HD patients has not been extensively researched. A previous study that explored this objective had a small sample size. Therefore, in this study, we compared the results of PB-PES implantation in HD and non-HD patients with symptomatic FPA diseases.

Methods

Study Design, Patient Population, and Eligibility

This study was a prospective, observational, single-center study of patients who had undergone PB-PES implantation. Between January 2019 and February 2020, 52 consecutive patients underwent PB-PES implantation for FPA. Of these, 29 patients were also undergoing HD and were classified into the HD cohort. The remaining 23 patients constituted the non-HD cohort. Clinical outcomes were compared between the HD and non-HD cohorts. The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the ethics committee of our hospital. All patients provided written informed consent for the EVT. The need for written informed consent for this publication was waived because of the observational study design. However, patients could opt out of the study. Patients were eligible for enrollment if they presented with symptomatic atherosclerotic FPA disease. The main exclusion criteria were nonatherosclerotic diseases or unsalvaged limbs.

Definitions

Chronic limb-threatening ischemia (CLTI) was defined as the presence of ischemic rest pain or ulcerations and/or gangrene. Major amputation was defined as an above-ankle amputation. The calcification severity was determined using the Peripheral Arterial Calcium Scoring System (PACSS) classification [8]. Angiographic and intravascular ultrasound (IVUS) parameters were evaluated by a cardiologist with sufficient expertise in peripheral artery disease. Incomplete stent expansion was defined as a minimum stent area (MSA) of ≤12 mm^2 [9]. The halo sign, as described by Bisdas et al [5, 10], was defined as a duplex ultrasound (DUS)-detected hypoechogenic area around the PB-PES. Stent thrombosis (ST) was defined as any thrombotic stent occlusion and was classified into three categories: early ST (0–30 days), late ST (LST, 30 days to 12 months), and very late ST (VLST, >12 months) [11].

Endovascular Procedure

Dual antiplatelet therapy (i.e., aspirin [100 mg/day] and clopidogrel [75 mg/day]) was administered before the procedure and continued for at least 6 months, followed by lifelong single-antiplatelet therapy (aspirin or clopidogrel). All EVT procedures were performed with the crossover approach from the contralateral common femoral artery by using a 6-Fr crossover sheath (Destination; Terumo, Tokyo, Japan). Unfractionated heparin (5000 units) was also routinely used. Calcification severity was evaluated, based on the PACSS grade, by using fluoroscopic images. The antegrade approach was performed with a 0.014-inch or 0.018-inch polymer-jacketed guidewire with the back-up support of a 4-Fr diagnostic catheter. A retrograde approach was used, if required. After passing the guidewire, IVUS was used to evaluate the vessel size and lesion morphology. Most target lesions were dilated with an optimally sized noncompliant balloon at a pressure of 20–24 atm. All balloon sizes were determined, based on the diameter of the external elastic membrane (EEM), as measured with IVUS. A cutting balloon (Peripheral Cutting Balloon; Boston Scientific) or a scoring balloon (NSE; NIPRO, Osaka, Japan) was used, if required. The combination strategy employing a drug-coated balloon was not included because it was not covered by the Japanese medical insurance system. Post-dilation was also administered to all patients by using the same noncompliant balloon. All PB-PESs were implanted in the patients by using the full-coverage stenting strategy, except for one patient with a case of in-stent (PF-PES) restenosis. After stenting, the MSA was evaluated by using IVUS. If the MSA was insufficient (i.e., ≤12 mm^2), additional post-dilatation using a 1-mm oversized high-pressure balloon was performed.

Follow-up Protocol

After PB-PES implantation, all patients were followed up at 1 month and 3 months, and every 3 months thereafter. The ankle brachial pressure index and DUS were measured at each follow-up visit. When DUS revealed the halo sign around the PB-PES, the diameter of the halo and blood flow within the halo were assessed.

Study Endpoints

The primary efficacy endpoint was the 12-month primary patency. The primary safety endpoint was the 12-month incidence of a major adverse cardiovascular and limb event (MACLE), which was defined as the composite of the incidences of all-cause death, major amputation, ST, and clinically driven target lesion revascularization (CD-TLR). Primary patency was defined as a peak systolic velocity ratio of <2.4 on DUS and the absence of DUS-detected stent occlusion. The rates of the following were compared as the secondary endpoints: overall survival (OS), limb salvage (LS), amputation-free survival (AFS), and freedom from CD-TLR and ST.

Statistical Analysis

Statistical analysis was conducted on an intention-to-treat basis. Continuous variables are expressed as the mean ± the standard deviation. Categorical variables are presented as the count (percentage). An unpaired *t*-test was used to compare continuous variables, whereas the chi-square test or Fisher's exact test was employed for categorical variables, as appropriate. Survival analyses were conducted using the Kaplan–Meier method to assess the primary and secondary outcomes. Statistical significance was defined as $P<0.05$. All statistical analyses were conducted using SPSS software (version 26; IBM Corporation, Somers, NY, USA).

Results

Patient and Lesion Characteristics

The baseline characteristics of the patients are shown in Table 1. The mean patient age was 75.5 years, and 80.8% of the patients were men. No characteristic differed significantly between the HD and non-HD cohorts, except for age (73.4 years vs. 78.2 years, $P=0.037$) and percentage of CLTI (65.5% vs. 26.1%, $P=0.005$). The lesion characteristics are shown in Table 2. The non-HD cohort, compared to the HD cohort, had longer lesions (24.8 cm vs. 18.3 cm, $P=0.024$) and more chronic total occlusion lesions (69.6% vs. 35.4%, $P=0.004$). By contrast, the HD cohort, compared to the non-HD cohort, had more PACSS grade 3 or 4 calcifications (79.3% vs. 47.8%, $P=0.047$). The procedural characteristics are shown in Table 2. Most lesions (92.3%) were dilated with noncompliant balloons. All lesions were treated with full-cover stenting, except for one lesion resulting from PF-PES restenosis. Noncompliant balloons were more frequently used in the HD cohort (100.0%) than in the non-HD cohort (82.6%), but the difference was not statistically significant ($P=0.071$). The scoring balloon was used significantly more frequently in the HD cohort than in the non-HD cohort (37.9% vs. 21.7%, $P=0.028$).

Table 1
Patients' background characteristics

	All cohort (*n*=52)	HD cohort (*n*=29)	Non-HD cohort (*n*=23)	*P*-value
Age (y)	75.5 ± 8.2	73.4 ± 8.7	78.2 ± 6.9	0.037
Male, *n* (%)	42 (80.8)	25 (86.2)	17 (73.9)	0.264
BMI, kg/m^2	21.1 ± 3.8	21.6 ± 4.0	20.5 ± 3.5	0.309
Ambulatory, *n* (%)	46 (88.5)	26 (89.7)	20 (86.9)	0.421
Hypertension, *n* (%)	41 (78.8)	22 (75.9)	19 (82.6)	0.554
Diabetes mellitus, *n* (%)	27 (51.9)	17 (58.6)	10 (43.5)	0.278
Dyslipidemia, *n* (%)	32 (61.5)	15 (51.7)	17 (73.9)	0.102
Smoking history, *n* (%)	37 (71.2)	20 (69.0)	17 (73.9)	0.744
Hemodialysis, *n* (%)	29 (55.8)	29 (100.0)	0 (0.0)	0.000
History of CAD, *n* (%)	23 (44.3)	13 (44.8)	10 (43.5)	0.680
History of CVD, *n* (%)	14 (26.9)	6 (20.7)	8 (34.7)	0.112
History of CHF, *n* (%)	5 (9.6)	2 (6.9)	3 (13.0)	0.455
CLTI, *n* (%)	25 (48.0)	19 (65.5)	6 (26.1)	0.005
Rutherford 2/3, *n* (%)	2 (3.8)/25 (48.1)	0 (0.0)/10 (34.5)	2 (8.7)/15 (65.2)	0.036
Rutherford 4/5/6, *n* (%)	10 (19.2)/13 (25.0)/2 (3.8)	7 (24.1)/11 (37.9)/1 (3.4)	3 (13.0)/2 (8.7)/1 (4.3)	0.036
Preprocedure ABI	0.59 ± 0.29	0.59 ± 0.34	0.60 ± 0.22	0.899
Postprocedure ABI	1.01 ± 0.15	1.00 ± 0.19	1.05 ± 0.09	0.210

HD, hemodialysis; BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; CHF, chronic heart failure; CLTI, chronic limb-threatening ischemia; ABI, ankle brachial pressure index

Table 2
Lesion characteristics

	All (*n*=52)	HD cohort (*n*=29)	Non-HD cohort (*n*=23)	*P*-value
Target lesion				
SFA alone, *n* (%)	29 (55.8)	17 (58.6)	12 (52.2)	0.642
Popliteal involved, *n* (%)	23 (44.2)	12 (41.4)	11 (47.8)	0.642
De novo lesion, *n* (%)	37 (71.2)	20 (69.0)	17 (73.9)	0.814
Restenosis: POBA/DCB/BNS/PF-PES, *n* (%)	4 (7.7)/6 (11.5) 4 (7.7)/1 (1.9)	2 (6.9)/3 (10.3)/3 (10.3)/1 (3.4)	2 (8.7)/3 (13.0) 1 (4.3)/0 (0.0)	0.814
Vessel diameter in QVA (mm)	5.9 ± 0.6	5.9 ± 0.7	5.9 ± 0.6	0.493
Lesion length in QVA (cm)	21.2 ± 11.9	18.3 ± 11.4	24.8 ± 11.6	0.046
CTO, *n* (%)	26 (50.0)	10 (34.5)	16 (69.6)	0.004
PACSS grade 3 or 4, *n* (%)	34 (65.4)	23 (79.3)	11 (47.8)	0.047
Procedure				
Use of scoring balloon, *n* (%)	16 (30.7)	11 (37.9)	5 (21.7)	0.028
Use of noncompliant balloon, *n* (%)	48 (92.3)	29 (100.0)	19 (82.6)	0.071
Full cover stenting, *n* (%)	51 (98.1)	28 (96.6)	23 (100.0)	0.369
Stent diameter (mm)	6.4 ± 0.5	6.4 ± 0.5	6.4 ± 0.5	0.713
Total stent length (cm)	23.0 ± 11.9	19.6 ± 10.7	27.3 ± 12.1	0.019
Stent/artery ratio	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.241
IVUS finding				
Distal EEM area (mm^2)	29.2 ± 8.5	31.2 ± 8.5	26.0 ± 4.6	0.074
MSA (mm^2)	20.1 ± 4.4	20.6 ± 4.6	19.1 ± 4.3	0.349
Incomplete stent expansion, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0.000
Follow-up DUS finding				
Halo sign, *n* (%)	15 (28.8)	8 (27.6)	7 (30.4)	0.822
Diameter of the halo (mm)	12.9 ± 2.9	11.3 ± 2.1	14.7 ± 2.7	0.019

HD, hemodialysis; SFA, superficial femoral artery; POBA, plain old balloon angioplasty; DCB, drug-coated balloon; BNS, bare nitinol stent; PF-PES, polymer-free paclitaxel-eluting stent; QVA, quantitative vessel angiography; CTO, chronic total occlusion; PACSS, Peripheral Artery Calcification Scoring System; IVUS, intravascular ultrasound; EEM, external elastic membrane; MSA, minimum stent area

The IVUS findings are shown in Table 2. The distal EEM area was 29.2 mm^2 and the MSA was 20.1 mm^2. Incomplete stent expansion (MSA≤12 mm^2) was not observed in this study. No significant differences existed between the HD and non-HD cohorts in the distal EEM area (31.2 mm^2 vs. 26.0 mm^2, *P*=0.074) or in the MSA (20.6 mm^2 vs. 19.1 mm^2, *P*=0.349).

During the follow-up period, the halo sign was observed in 15 (28.8%) patients (mean diameter: 12.9 mm). In these patients, no flow was detected within the halo area, and all patients were asymptomatic. No significant difference existed between the HD and non-HD cohorts in the incidence of the halo sign (27.6% vs. 30.4%, *P*=0.822).

Endpoints

The median follow-up duration was 17.1 months (interquartile range: 12.1-20.5). The overall primary patency rate was 93.3% (Figure 1A, Table 3). No significant difference existed in the primary patency between the HD and non-HD cohorts (91.7% vs. 95.0%, *P*=0.577; Figure 1B and Table 3). The overall incidence rate of MACLE was 16.6%, and no significant difference existed between the HD and non-HD cohorts (20.2% vs. 13.3%, *P*=0.954; Table 3).

Table 3
Primary and secondary endpoints (at the 12-month follow-up)

	All cohort (n=52)	HD cohort (n=29)	Non-HD cohort (n=23)	*P*-value
Primary patency (%)	93.3	91.7	95.0	0.577
MACLE rate (%)	16.6	20.2	13.3	0.954
Overall survival rate (%)	89.8	87.9	91.3	0.952
Limb salvage rate (%)	100.0	100.0	100.0	0.000
AFS rate (%)	89.8	87.9	91.3	0.952
Freedom from CD-TLR rate (%)	93.3	91.7	95.0	0.819
Stent thrombosis rate (%)	6.7	8.3	5.0	0.956

HD, hemodialysis; MACLE, major adverse cardiovascular and limb event; AFS, amputation-free survival; CD-TLR, clinically driven target lesion revascularization

The OS, LS, AFS, freedom from CD-TLR, and ST rates were 89.8%, 100.0%, 89.8%, 93.3%, and 6.7%, respectively (Table 3). No significant differences existed between the HD and non-HD cohorts in any of the secondary outcomes. Detailed information on patients with ST is shown in Table 4.

Table 4
Characteristics of patients with ST

Patient No.	Age (y), sex	HD status	No. days to ST (ST type)	Location, length	Antiplatelet therapy at ST	Halo sign (size [mm])	Clinical presentation	Imaging	Suspected cause of ST	Treatment
Case 1	60, Male	Non-HD	195 (LST)	SFA to POP, 18 cm	Aspirin + clopidogrel	Not detected	Sudden onset rest pain	OFDI and angioscopy	LASM	Aspiration, thrombolysis, and POBA
Case 2	72, Male	Non-HD	190 (LST)	SFA, 20 cm	Aspirin + clopidogrel	Not detected	Sudden onset rest pain	OFDI and angioscopy	Calcified nodule	Thrombolysis and stenting
Case 3	75, Female	HD	237 (LST)	SFA 33 cm	Aspirin + clopidogrel	Detected (10 mm)	Sudden onset rest pain	OFDI	LASM	Aspiration and POBA
Case 4	75, Female	HD	548 (VLST)	SFA to POP 34 cm	Aspirin + clopidogrel	Detected (15 mm)	Sudden onset rest pain	OFDI	LASM	Thrombolysis and stent graft implantation
Case 5	87, Female	Non-HD	400 (VLST)	SFA to POP 40 cm	Aspirin + clopidogrel	Detected (10 mm)	Gradually appearing rest pain	None	Unknown	Untreated
Case 6	76, Female	HD	597 (VLST)	SFA, 12 cm	Aspirin + clopidogrel	Not detected	Sudden onset of severe claudication	IVUS	LASM	Aspiration and DCB

ST, stent thrombosis; HD, hemodialysis; LST, late stent thrombosis; VLST, very late stent thrombosis; LASM, late-acquired stent malposition; OFDI, optical frequency domain imaging; POBA, plain old balloon angioplasty; POP, popliteal artery; SFA, superficial femoral artery; IVUS, intravascular ultrasound; DCB, drug-coated balloon

Representative Case of ST (Late ST)

A male patient in his 70s with left ischemic rest pain due to severely calcified distal FPA occlusion (Figure 3A) received two PB-PES implantations (Figure 3B). The symptoms resolved completely after the procedure. Six months after the EVT, the patient complained of sudden leg pain. ST was suspected. Angiography revealed occlusion of the PB-PES (Figure 3C). Catheter thrombectomy and thrombolysis with a continuous infusion of urokinase (480,000 IU/day) was administered for 2 days. The angiogram obtained after thrombolysis is shown in Figure 3D. Optical frequency domain imaging (OFDI) revealed late-acquired stent malapposition (LASM) of the PB-PES (Figure 3E). The pathologic evaluation of the aspirated thrombus revealed eosinophilic infiltration in the fibrin/platelet-rich thrombus, which suggested an allergic reaction (Figure 4).

As shown in Table 4, we encountered three cases of LST and three cases of VLST. In two cases in LST and two cases of VLST, LASM has also been observed. In another case, ST was caused by calcified nodule progression beyond the stent strut [12]. Dual antiplatelet therapy was continued in all 6 cases of ST.

Discussion

The aim of this study was to compare the clinical performance of PB-PESs between HD and non-HD patients with symptomatic FPA disease. To our knowledge, the effectiveness of PB-PES in hemodialysis (HD) patients has not been reported. Therefore, we believe that this paper is the

first report on the results of PB-PES implantation in patients undergoing HD. The acceptable safety and outstanding patency of PB-PES in HD patients was comparable to the results in non-HD patients. This finding suggested that primary PB-PES implantation may be an acceptable strategy for HD patients.

The PB-PES has shown good 12-month primary patency in previous studies (MAJESTIC study [13]: 96%; IMPERIAL study [4]: 86.8%). However, none of these studies included patients who were undergoing HD. PB-PESs has also shown sufficient patency in real-world target populations (Bisdas et al. [5]: 1-year primary patency, 87%; Stavroulakis et al. [10]: 2-year primary patency, 71%; and Kum et al. [6]: 1-year primary patency, 84%); however, these studies did not include enough HD patients to provide a robust result. Thus, the efficacy and safety of PB-PES in patients undergoing HD remain unclear. Therefore, we verified the efficacy and safety of PB-PES in HD patients.

In our study, an outstanding primary patency rate of 93.3% was reported in the overall cohort. Direct comparison with existing literature is impossible; however, the primary patency rate in our study was higher than those in previous reports [4–6]. The reason for this difference is unclear. It may be because of the use of IVUS-guided procedures. To avoid insufficient stent expansion, aggressive pre- and post-dilatation with an adequate size balloon, as confirmed with IVUS, was conducted for all procedures. Therefore, the HD and non-HD cohorts had sufficient MSA (20.6 mm^2 vs. 19.1 mm^2) and favorable primary patency (91.7% vs. 95.0%, P=0.577). This result suggests that PB-PES is also effective in HD patients.

Bisdas et al. [5] observed the halo sign, which is a hypoechoic area around the stent, confirmed with DUS, in five (8%) patients in their 1-year report. No blood flow was observed in the halo area. One of the five patients developed ST and presented with acute limb ischemia. In a 2-year report [10], the halo sign was observed more frequently (20%), but blood flow in the halo was rare (only two patients). After the reports publication, the halo sign became a cause of concern after PB-PES implantation. Similar observations were also reported in the 2-year results of the IMPERIAL trial [14]. We reported the IVUS, OFDI, and angioscopy findings of the halo sign, which were observed 3 months after PB-PES implantation. These imaging findings are not indicative of a true aneurysmal formation around the PB-PES [15].

Immunobiological examination and magnetic resonance imaging revealed inflammation of the vessel wall [5]. Therefore, the halo sign may be a result of an inflammatory response caused by the interventional procedures (i.e., ballooning or stenting) and/or an inflammatory or allergic reaction to the stent components (e.g., stent platform, polymer, and/or paclitaxel). The nature of this phenomenon remains unclear.

In our study, halo signs were observed in 28.8% of patients with no significant difference between the HD and non-HD cohorts (27.6% vs. 30.4%, P=0.822). The incidence of halos was slightly higher than that reported in previous studies [5, 10, 14]. IVUS-guided aggressive dilatation may have affected these phenomena.

Stavroulakis et al. [10] also reported the angiographic findings of a case of LASM and its related ST. In our study, four cases of LASM and their related STs were confirmed with OFDI or IVUS after the onset of ST (Table 4). The halo sign was only observed in two of the four cases. In the field of coronary intervention, LASM is occasionally observed after the implantation of drug-eluting stents (especially first-generation drug-eluting stents) and may be caused by allergic reactions to drugs (e.g., limus or paclitaxel) and/or polymers, and/or reactions to vasodilation. In the pathological findings of our ST case, eosinophils were observed in the aspirated thrombus. This finding suggested that an allergic reaction may be associated with LASM and its related thrombus. Further collection of thrombi and their pathological evaluation are needed to confirm this hypothesis.

No scientific data exist regarding the relationship between the halo sign and LASM (and LASM-related ST). Careful follow-up is necessary to determine their relationship and confirm the long-term safety of PB-PES.

This study had some important limitations. First, it was a small single-center study. Multicenter studies with larger populations are needed to confirm the results of our study. Each event was evaluated using site analysis. An independent core laboratory is necessary for the precise evaluation of each event.

Conclusions

PB-PES shows exceptional 1-year primary patency and acceptable safety in HD and non-HD patients. Further investigation with a longer follow-up should be conducted to investigate the association between the halo sign and the incidence of ST.

Abbreviations

AFS, amputation-free survival; CLTI, chronic limb-threatening ischemia; DUS, duplex ultrasound; EEM, external elastic membrane; EVT, endovascular therapy; FPA, femoropopliteal artery; IVUS, intravascular ultrasound; LASM, late-acquired stent malapposition; LS, limb salvage; LST, late stent thrombosis; MACLE, major adverse cardiovascular and limb event; MSA, minimum stent area; OFDI, optical frequency domain

imaging; OS, overall survival; PACSS, Peripheral Arterial Calcium Scoring System; PB-PES, polymer-based paclitaxel-eluting stent; ST, stent thrombosis; VLST, very late stent thrombosis

Declarations

Ethics approval and consent to participate: The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the ethics committee of our hospital. The need for written informed consent from the patients was waived owing to the observational study design.

Consent for publication: Not applicable.

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: TN is a consultant of, Boston Scientific (Maple Grove MN, USA), Century Medical Inc. (Tokyo, Japan), COOK Medical (Bloomington, IN, USA), Cordis Cardinal Health (Santa Clara, CA, USA), Kaneka Medix (Tokyo, Japan), Medicon (Tokyo, Japan), NIPRO (Osaka, Japan), and OrbusNeich Japan (Tokyo, Japan).

Funding: None.

Authors' contributions:

TN, ST, KO, and HW made a concept of this study. TN and SK wrote this manuscript. ST did a pathological evaluation. TN, SK, MM, JA, YA, KA, HT, and KO did endovascular procedures and data collection. MM and JA made Figures and Tables. HT did statistical analysis. All authors read and approved the final manuscript.

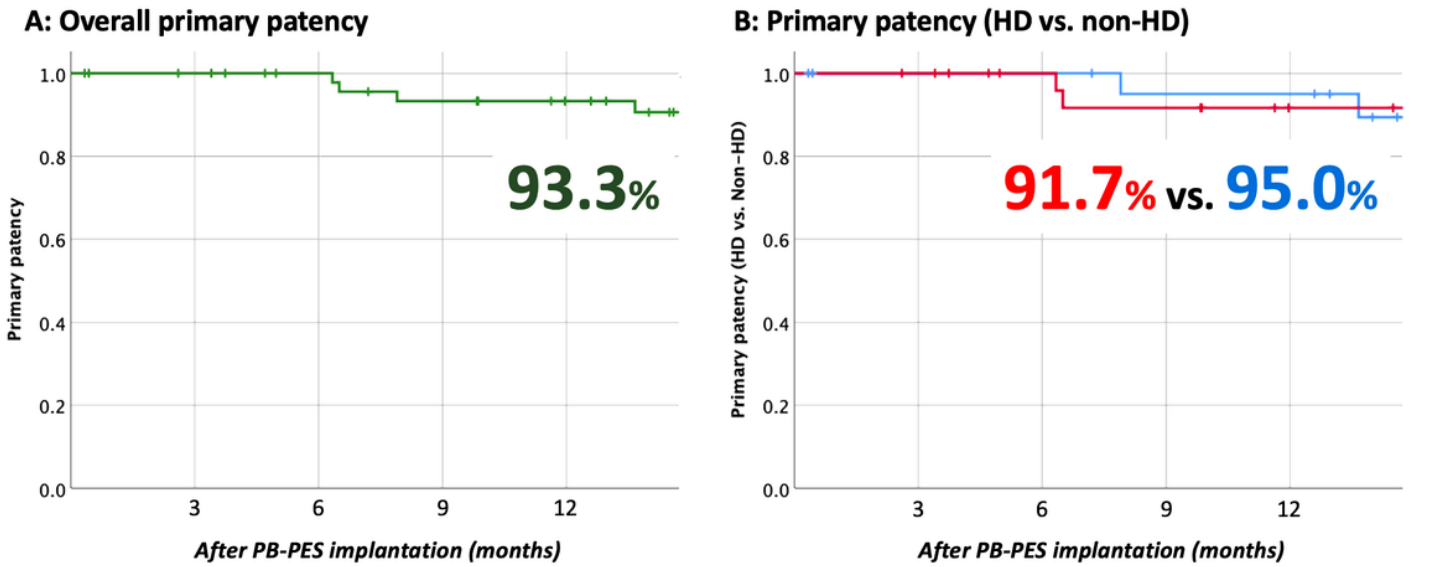
Acknowledgements: Not applicable.

References

1. Aboyans V, Ricco JB, Bartelink MEL et al (2018) 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries endorsed by the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 39:763–816
2. Feldman DN, Armstrong EJ, Aronow HD, Gigliotti OS, Jaff MR, Klein AJ et al (2018) SCAI consensus guidelines for device selection in femoral-popliteal arterial interventions. Catheter Cardiovasc Interv 92:124–140
3. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB et al (2016) Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. Circulation 133:1472–1483 discussion 1483
4. Gray WA, Keirse K, Soga Y, Benko A, Babaev A, Yokoi Y et al (2018) A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. Lancet 392:1541–1551
5. Bisdas T, Beropoulis E, Argyriou A, Torsello G, Stavroulakis K (2018) 1-year All-Comers analysis of the Eluvia drug-eluting stent for long femoropopliteal lesions after suboptimal angioplasty. JACC Cardiovasc Interv 11:957–966
6. Kum S, Ipema J, Huizing E, Tan YK, Lim D, Lok IY et al (2021) Outcomes of the paclitaxel-eluting Eluvia stent for long femoropopliteal lesions in Asian patients with predominantly chronic limb-threatening ischemia. Vasc Med 26:267–272
7. Chou HH, Huang HL, Hsieh CA, Jang SJ, Tzeng IS, Ko YL (2018) Drug-coated balloon vs. conventional balloon angioplasty in dialysis patients with symptomatic femoropopliteal disease—a matched comparison. Circ J 82:1908–1916
8. Rocha-Singh KJ, Zeller T, Jaff MR (2014) Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. Catheter Cardiovasc Interv 83:E212–E220
9. Iida O, Takahara M, Soga Y, Nakano M, Yamauchi Y, Zen K et al (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

10. Stavroulakis K, Torsello G, Bosiers M, Argyriou A, Tsilimparis N, Bisdas T (2021) 2-year outcomes of the Eluvia drug-eluting stent for the treatment of complex femoropopliteal lesions. JACC Cardiovasc Interv 14:692–701
11. Kuramitsu S, Ohya M, Shinozaki T, Otake H, Horie K, Kawamoto H et al (2019) Risk factors and long-term clinical outcomes of second-generation drug-eluting stent thrombosis. Circ Cardiovasc Interv 12:e007822
12. Nakama T, Saito A, Obunai K, Azumi Y et al (2020) Calcified nodule progression-related stent thrombosis after polymer-based paclitaxel-eluting nitinol stent implantation for femoropopliteal artery. J Vasc Surg Cases Innov Tech 7:510–511
13. Müller-Hülsbeck S, Keirse K, Zeller T, Schroë H, Diaz-Cartelle J (2016) Twelve-month results from the MAJESTIC trial of the Eluvia paclitaxel-eluting stent for treatment of obstructive femoropopliteal disease. J Endovasc Ther 23:701–707
14. Müller-Hülsbeck S, Benko A, Soga Y, Fujihara M, Iida O, Babaev A et al (2021) Two-year efficacy and safety results from the IMPERIAL randomized study of the eluvia polymer-coated drug-eluting stent and the Zilver PTX polymer-free drug-coated stent. Cardiovasc Intervent Radiol 44:368–375. doi: 10.1007/s00270-020-02693-1
15. Nakama T, Obunai K, Muraishi M, Azumi Y, Watanabe H (2020) Angiographic and intravascular imaging findings for ultrasound detected aneurysmal degeneration following polymer-based paclitaxel eluting nitinol stent implantation for femoropopliteal artery occlusion. EJVES Vasc Forum 47:3–5. doi: 10.1016/j.ejvsvf.2020.02.009

Figures



Months	0	3	6	9	12
No. at risk	52	49	45	41	37
%	100.0	100.0	100.0	93.3	93.3
% SE	0.0	0.0	0.0	3.7	3.7

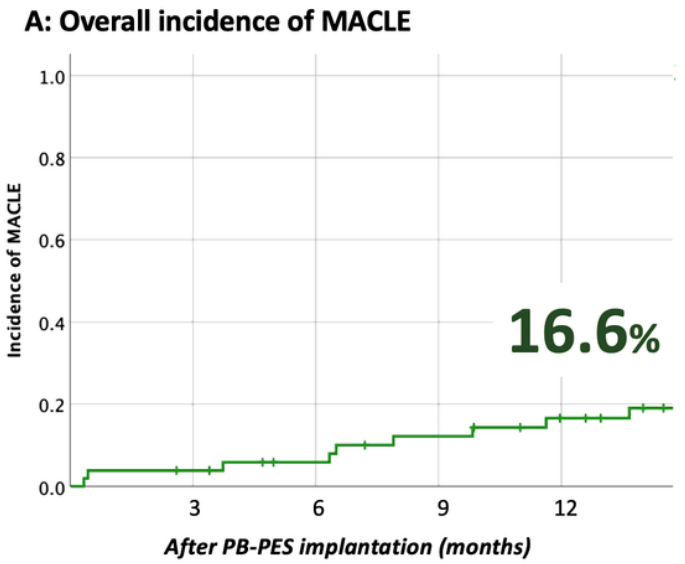
	Months	0	3	6	9	12
HD cohort	No. at risk	29	28	24	22	18
	%	100.0	100.0	100.0	91.7	91.7
	% SE	0.0	0.0	0.0	5.6	5.6
Non-HD cohort	No. at risk	23	21	21	19	19
	%	100.0	100.0	100.0	95.0	95.0
	%SE	0.0	0.0	0.0	4.9	4.9

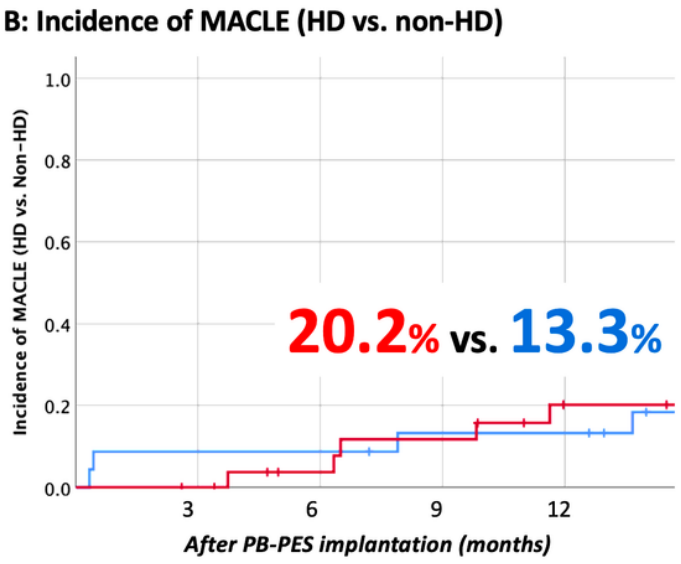
Figure 1

Primary patency

The overall primary patency rate is 93.3% (**A**). The primary patency between the HD and non-HD cohorts is not significantly different (91.7% vs. 95.0%, *P*=0.577) (**B**).

HD, hemodialysis; PB-PES, polymer-based paclitaxel-eluting stent; %SE, percent standard error





Months	0	3	6	9	12
No. at risk	52	49	45	41	37
%	0.0	3.8	5.8	12.2	16.6
% SE	0.0	2.7	3.3	4.7	5.4

	Months	0	3	6	9	12
HD cohort	No. at risk	29	28	24	22	17
	%	0.0	0.0	3.7	11.7	20.2
	% SE	0.0	0.0	3.6	6.4	8.1
Non-HD cohort	No. at risk	23	21	21	19	18
	%	0.0	8.7	8.7	13.3	13.3
	%SE	0.0	5.9	5.9	7.1	7.1

Figure 2

The incidence rate of MACLE

The overall incidence rate of MACLE is 16.6% (**A**). The incidence rate of MACLE between the HD and non-HD cohorts is not significantly different (20.2% vs. 13.3%, *P*=0.954) (**B**).

MACLE, major adverse cardiovascular and limb event; HD, hemodialysis; PB-PES, polymer-based paclitaxel-eluting stent

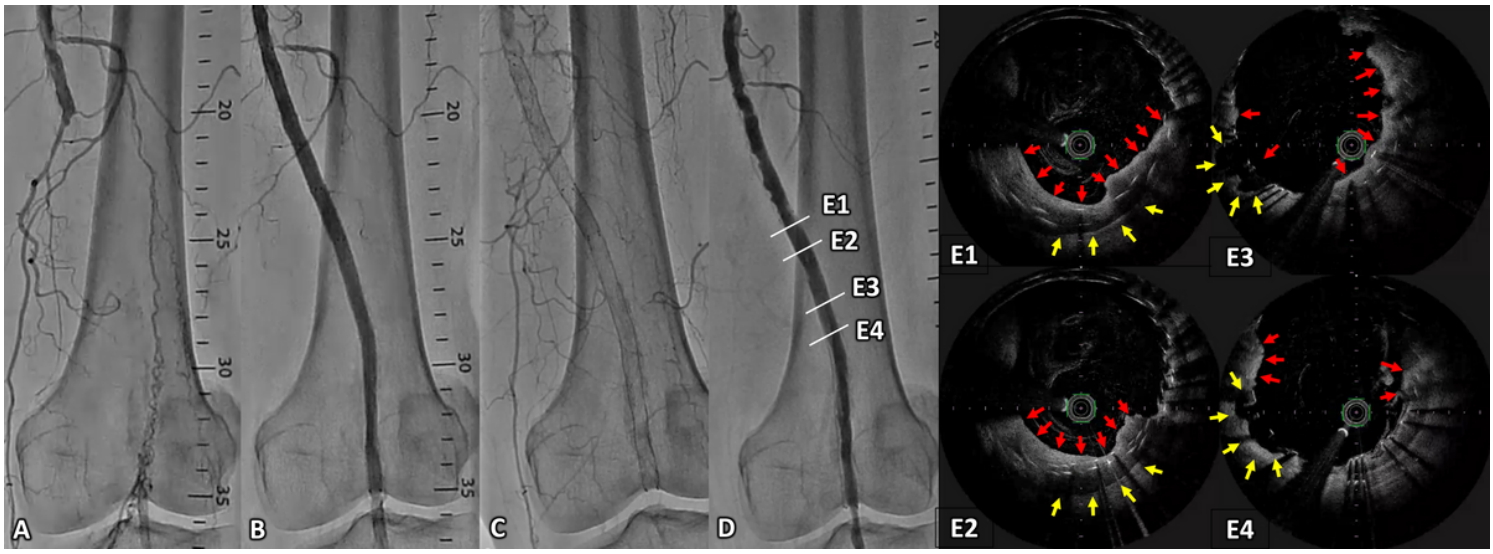


Figure 3

A representative case of stent thrombosis after PB-PES implantation

A male patient in his 70s with ischemic rest pain in his left leg due to a severely calcified distal FPA occlusion (**A**). He received two PB-PES implants (**B**). Angiography after ST reveals the occlusion of the PB-PES (**C**). The angiogram findings after the patient underwent thrombectomy and thrombolysis with 480,000 IU/day urokinase (**D**). Optical frequency domain imaging findings after thrombolysis (**E1-E4**). In (E), the residual thrombus is indicated by red arrows and the LASM of the PB-PES is indicated by yellow arrows.

PB-PES, polymer-based paclitaxel-eluting stent; FPA, femoropopliteal artery; ST, stent thrombosis; LASM, late-acquired stent malapposition

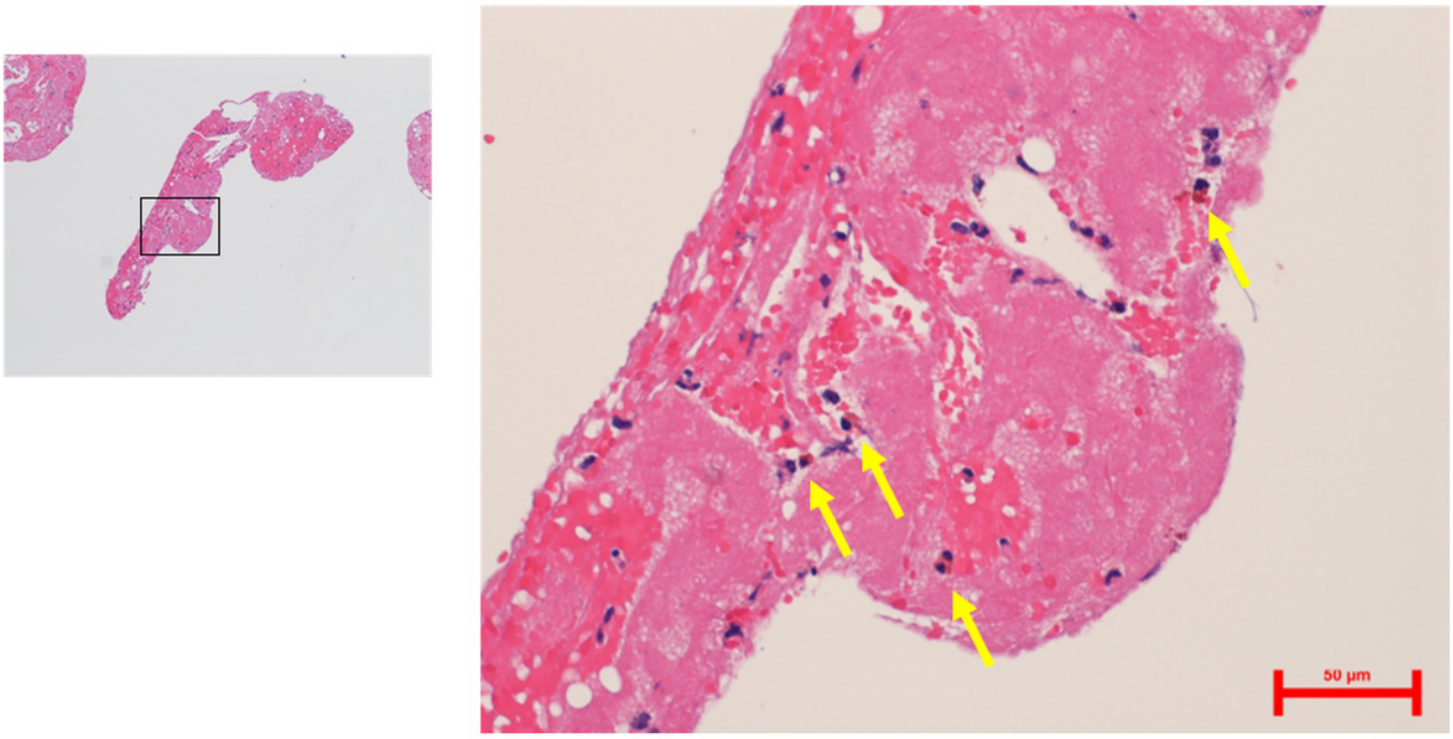


Figure 4

Pathological findings of the aspirated thrombus

The left image shows the aspirated thrombus sample stained with hematoxylin and eosin. The right image is the magnification of the boxed area on the left. The pathological evaluation reveals many eosinophils in the aspirated thrombus (yellow arrows; in the magnification image).