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Comparison of High-Dose versus Low-Dose Paclitaxel Drug-Coated Balloons for Native Femoropopliteal Artery Disease: An Analysis of the K-VIS ELLA Registry

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Purpose: Drug-coated balloons (DCBs) have demonstrated favorable outcomes in the treatment of femoropopliteal artery (FPA) disease. A variety of DCBs are currently available, with differing doses of antiproliferative agents and types of excipients. The objective of this study was to compare the efficacy and safety of high-dose versus low-dose paclitaxel DCBs for the treatment of FPA disease.

Materials and Methods: We analyzed data from the multicenter the Korean Vascular Intervention Society Endovascular Therapy in Lower Limb Artery Diseases (K-VIS ELLA) registry, focusing on patients treated with a high-dose paclitaxel DCB (IN.PACT™) or low-dose paclitaxel DCB (Lutonix™ or Ranger™) for native vessel FPA disease. We used inverse probability of treatment weighting to adjust for confounding factors and conducted subgroup analyses based on lesion characteristics.

Results: Among 820 target limbs, 626 were treated with a high-dose paclitaxel DCB, and 194 were treated with a low-dose paclitaxel DCB. At 12 months, there were no significant differences in rates of freedom from clinically driven target lesion revascularization (TLR; 91.7% vs. 89.4%, log-rank p=0.35), major adverse limb event (MALE; 91.4% vs. 89.0%, log-rank p=0.31), or all-cause mortality (93.1% vs. 93.8%, log-rank p=0.79) between high-dose and low-dose groups. On multivariable analysis, the presence of chronic heart failure and chronic kidney disease were the only independent predictors of clinically driven TLR after DCB treatment.

Conclusion: In this multicenter cohort study of patients with complex FPA disease, there were no significant differences between high-dose DCB and low-dose DCB with respect to freedom from clinically driven TLR, MALE, or all-cause mortality at 12-month follow-up.

Trial registration: ClinicalTrials.gov Identifier : NCT02748226

Key Words: Peripheral artery disease, popliteal artery, balloon angioplasty, paclitaxel

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INTRODUCTION

Femoropopliteal artery (FPA) disease commonly manifests as long, calcified, or totally occluded lesions, presenting significant challenges for effective treatment via endovascular techniques.[1] The femoral and popliteal arteries are subjected to various external forces during leg movements, which can negatively impact the outcomes of endovascular therapy (EVT),[2] and implantation of long stents is associated with an increased risk of restenosis.[3] Drug-coated balloons (DCBs) are engineered to deliver antiproliferative drugs directly to the arterial wall during angioplasty, reducing the likelihood of restenosis. Unlike stents, DCBs do not involve the use of a permanent implant, thereby minimizing the risk of long-term complications, such as stent fracture or late stent thrombosis. Moreover, by avoiding a permanent scaffold, DCBs may facilitate more natural blood flow dynamics and vessel movement. This is particularly advantageous in anatomically complex regions, such as FPA segments subjected to frequent flexion and extension leg movements. DCBs have exhibited favorable clinical outcomes in several clinical trials.[4-6]

A diverse array of DCBs have entered the market. In Korea, three DCBs are commonly used in clinical practice: IN.PACT™ (Medtronic Inc., Santa Rosa, CA, USA; 3.5 μg/mm^2 paclitaxel+urea), Lutonix™ (Becton Dickinson, Franklin Lakes, NJ, USA; 2.0 μg/mm^2 paclitaxel+polysorbate+sorbitol), and Ranger™ (Boston Scientific, Marlborough, MA, USA; 2.0 μg/mm^2 paclitaxel+acetyl tributyl citrate). Despite variations in paclitaxel dose and excipients, all have demonstrated clinical efficacy and safety in treating FPA disease.[7-10] However, the limited number of studies comparing different DCBs have reported discrepant findings.[11-13] In this study, we compared the clinical outcomes of high-dose paclitaxel DCB (IN.PACT) versus low-dose paclitaxel DCBs (Lutonix and Ranger) in patients with FPA disease utilizing data from a multicenter registry.[14]

MATERIALS AND METHODS

Study population

Study participants were selected from the Korean Vascular Intervention Society Endovascular Therapy in Lower Limb Artery Diseases Registry (K-VIS ELLA) registry, a multicenter (19 centers) database containing retrospective and prospective cohorts of patients with lower extremity artery disease treated with EVT.

Among the 4393 limbs included in the registry, we identified 1320 limbs treated with DCB for FPA disease. After excluding 29 limbs previously treated with bypass surgery, 202 limbs undergoing nonsurgical reintervention of the same target lesions, 17 limbs treated with other DCBs, and 252 limbs with insufficient data, we included 820 limbs in the present analysis. Of the included limbs, 626 were treated with a high-dose DCB and 194 were treated with a low-dose DCB (Lutonix, n=112; Ranger, n=82) (Fig. 1).

The K-VIS ELLA registry is registered at ClinicalTrials.gov

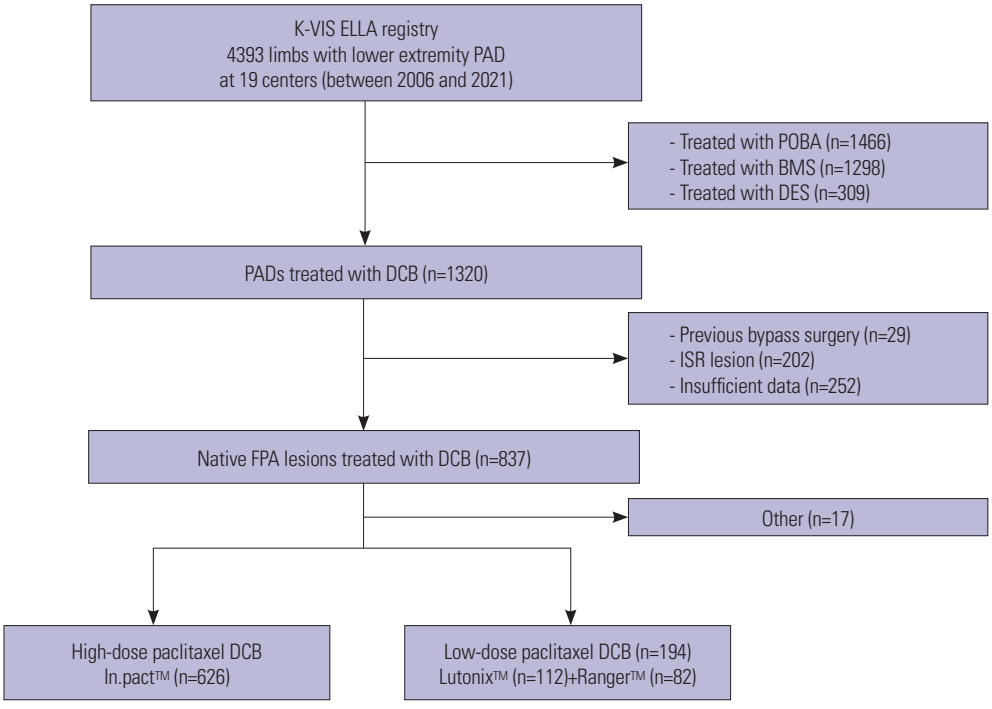

Fig. 1. Study flowchart. BMS, bare metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; FPA, femoropopliteal artery; ISR, in-stent restenosis; K-VIS ELLA, the Korean Vascular Intervention Society Endovascular Therapy in Lower Limb Artery Diseases; PAD, peripheral artery disease; POBA, plain old balloon angioplasty.

(NCT02748226). The current study was approved by the Institutional Review Board at each participating center and complied with the principles of the Declaration of Helsinki as revised in 2013 (Yonsei University Health System, Severance Hospital, IRB approval number: 4-2013-0463). Written informed consent was waived for retrospective cohort participants but obtained from all prospectively enrolled participants.

Data collection

Clinical, lesion, and procedure data were collected retrospectively and prospectively. Baseline clinical data included patient demographics, comorbidities, prior EVT or minor amputation, severity of peripheral arterial disease based on the Rutherford category, medication use, and pre-procedural ankle-brachial index (ABI). Lesion data included the lesion length, severity of calcification, and distribution of FPA lesions based on the TransAtlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC)-II system and consensus definitions from the Peripheral Academic Research Consortium.[15,16] Procedure data included the type of DCB, subintimal wiring approach, use of atherectomy, concomitant treatment of infrapopliteal arteries, and number of below-the-knee runoff vessels. Complications during or shortly after EVT were recorded. Patients were followed clinically at 1, 6, and 12 months after the index procedure and thereafter at intervals of either 6 or 12 months.

Endovascular procedure

All endovascular procedures were performed by interventional cardiologists, and the intervention strategy, device selection, and decision to perform pre-treatment adjunctive atherectomy in select patients were left to the operators' discretion. For revascularization of FPA lesions, intraluminal wiring with a 0.018- or 0.035-inch guidewire was favored, but a subintimal approach with re-entry into the distal true lumen was used when intimal wire passage failed. Pre-dilation with a plain balloon was performed routinely before DCB use, except for limbs initially treated with atherectomy. FPA target lesions were treated with either a high-dose paclitaxel DCB (IN.PACT) or a low-dose paclitaxel DCB (Lutonix or Ranger). DCBs were inflated for 180 seconds. After DCB treatment, follow-up angiography was performed. If angiography revealed flow-limiting dissection or residual stenosis ≥30%, additional balloon dilation or provisional stenting was performed. After the procedure, all patients received dual antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day) for at least 6 months, unless contraindicated. Cilostazol was used at the operators' discretion.

Study endpoints

The primary endpoint was freedom from clinically driven target lesion revascularization (TLR) at 12 months after the index procedure, which was defined as reintervention within 5 mm proximal or distal to the treated segment for >50% angiographic diameter stenosis with concomitant worsening symptoms and a decrease in ABI >0.15, compared with the immediate post-procedural ABI. Secondary endpoints were freedom from major adverse limb events (MALEs) and all-cause death at 12 months. MALEs were defined as the composite of any major amputation (above-ankle or below-the-knee), repeat revascularization of the target limb via EVT, surgical bypass, or endarterectomy.

Statistical analysis

Continuous variables are presented as mean±standard deviation, and categorical variables are presented as count (percentage). Inverse probability of treatment weighting (IPTW) was applied to adjust for confounding factors that may affect device selection. The following variables were included in the IPTW model: age, sex, body mass index, current smoker, hypertension, diabetes mellitus, dyslipidemia, chronic heart failure, chronic kidney disease, coronary artery disease, stroke, clinical presentation [claudication vs. chronic limb-threatening ischemia (CLTI)], lesion length, popliteal artery involvement, moderate or severe calcification, total occlusion, pre-procedural ABI, and medication(s) at post-procedure discharge (Supplementary Fig. 1, only online). Mean standard difference was determined for baseline clinical and procedure characteristics, with a cut-off value of 0.1 indicating well-balanced groups. Baseline clinical and procedure characteristics were compared with Welch's t-test for continuous variables and χ^2-tests for categorical variables using both crude and IPTW data.

Primary and secondary endpoints were estimated using Kaplan–Meier survival analysis and compared using the log-rank test. Cox proportional hazard regression was performed to investigate the predictors of TLR after DCB treatment, and fully adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for study outcomes using multivariable Cox regression. Previously reported factors associated with patency loss (defined clinically and/or via diagnostic testing) were included in the multivariable Cox regression model, and regression analyses were performed with both crude and IPTW data.[17-20]

Subgroup analyses were performed according to the TASC-II classification, and we also compared the outcome event rates for each device.

All analyses were two-sided, with a p value<0.05 considered statistically significant. All data analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline clinical characteristics

Baseline clinical characteristics of the high-dose DCB group (n=626) and low-dose DCB group (n=194) are summarized in Table 1. Baseline clinical characteristics were similar between

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groups, except diabetes mellitus was less frequent in the high-dose group than in the low-dose group (65.0% vs. 73.3%, p=0.030). After IPTW, clinical characteristics were balanced between the high-dose and low-dose groups, with a standardized mean difference of <0.1 for all variables. Mean patient age was 69 years, and the majority of patients were male (81%). Approximately 68% and 31% of patients had diabetes mellitus and chronic kidney disease, respectively, and CLTI was present in 38% of study participants.

Target lesion and procedural data

Regarding target lesion characteristics, the high-dose DCB group had longer lesions (mean, 192.7 mm vs. 164.6 mm, p=0.002) and more frequent popliteal artery involvement (32.3% vs. 19.6%, p=0.001) compared to the low-dose DCB group. After IPTW, all target lesion characteristics were well-balanced between groups, except for the target lesion location. Post-procedural technical success rates were similar between groups (high-dose vs. low-dose: 97.3% vs. 94.8%, p=0.152) (Table 2). Procedure-related complications also did not differ between the high-dose and low-dose DCB groups.

Clinical outcomes

Patients were followed for a mean duration of 414.4±260.5 days. The primary endpoint of 12-month freedom from clinically driven TLR did not differ between the high-dose DCB group and the low-dose DCB group (92.1% vs. 90.2%, p=0.25) after IPTW (Table 3, Figs. 2 and 3). The 12-month mortality rates were also similar between groups [high-dose vs. low-dose: 6.9% (n=34) vs. 6.2% (n=9)]. Freedom from MALE (high-dose vs. low-dose: 91.4% vs. 89.0%, log-rank p=0.31) and freedom from all-cause mortality (high-dose vs. low-dose: 93.1% vs. 93.8%, log-rank p=0.79) at 12 months were also comparable between groups. Two major amputation events were observed in each treatment group (high-dose vs. low-dose: 0.3% vs. 1.7%, p=0.20).

Primary and secondary outcomes were not significantly different among the three DCB products (Supplementary Figs. 2–4, only online). When comparing clinical outcomes according to TASC-II classification, the high-dose and low-dose DCB groups showed similar rates of freedom from TLR, and the results remained consistent after excluding limbs that underwent provisional stenting (Supplementary Figs. 5 and 6, only online). As shown in Table 4, the type of DCB (high-dose vs. low-dose)

Table 1. Baseline Clinical Characteristics Before and After Inverse Probability of Treatment Weighting

Variables	Before IPTW				After IPTW		
	High-dose DCB (n=626)	Low-dose DCB (n=194)	*p* value	SMD	High-dose DCB (n=625.8)	Low-dose DCB (n=196.6)	SMD
Age, yr	69.1±10.9	69.2±10.5	0.885	0.012	69.1±10.9	69.3±10.7	0.017
Sex, male	502 (80.2)	159 (82.0)	0.660	0.045	505.0 (80.7)	158.5 (80.6)	0.002
BMI, kg/m^2	23.7±3.9	23.2±3.5	0.160	0.119	23.6±3.8	23.8±3.8	0.069
Current smoker	164 (26.4)	43 (22.8)	0.361	0.085	156.9 (25.1)	43.3 (22.0)	0.072
Hypertension	469 (74.9)	146 (75.3)	>0.999	0.008	468.5 (74.9)	148.0 (75.3)	0.010
Diabetes mellitus	407 (65.0)	143 (73.7)	0.030	0.186	419.8 (67.1)	133.2 (67.7)	0.014
Dyslipidemia	404 (64.5)	125 (64.4)	>0.999	0.002	404.2 (64.6)	130.8 (66.5)	0.040
CKD	186 (29.7)	68 (35.1)	0.188	0.114	193.4 (30.9)	58.3 (29.7)	0.027
ESRD	100 (16.0)	34 (17.5)	0.690	0.042	103.0 (16.5)	28.3 (14.4)	0.057
Chronic heart failure	32 (5.1)	7 (3.6)	0.505	0.074	29.6 (4.7)	7.5 (3.8)	0.045
CAD	273 (43.6)	79 (40.7)	0.337	0.059	268.0 (42.8)	82.6 (42.0)	0.017
Previous stroke	100 (16.0)	37 (19.1)	0.368	0.082	102.9 (16.4)	28.6 (14.6)	0.052
Symptoms			0.310	0.090			0.027
Claudication	389 (62.1)	112 (57.7)			382.9 (61.2)	122.9 (62.5)	
CLTI	237 (37.9)	82 (42.3)			242.9 (38.8)	73.7 (37.5)	
Pre-procedure ABI	0.60±0.19	0.63±0.18	0.062	0.156	0.61±0.19	0.60±0.19	0.055
Previous EVT	233 (37.2)	71 (36.6)	0.943	0.013	234.4 (37.5)	71.4 (36.3)	0.024
Previous amputation	41 (6.5)	14 (7.3)	0.859	0.028	44.0 (7.0)	14.4 (7.4)	0.013
Medications at discharge							
Aspirin	529 (84.5)	148 (76.3)	0.012	0.208	518.1 (82.8)	166.0 (84.4)	0.043
Clopidogrel	527 (84.2)	153 (78.9)	0.107	0.137	520.5 (83.2)	167.4 (85.2)	0.054
Cilostazol	183 (29.2)	52 (26.8)	0.573	0.054	177.8 (28.4)	48.4 (24.6)	0.086
Statin	490 (78.3)	136 (70.1)	0.025	0.188	476.8 (76.2)	150.4 (76.5)	0.006

ABI, ankle-brachial index; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CLTI, chronic limb-threatening ischemia; DCB, drug-coated balloon; ESRD, end-stage renal disease; EVT, endovascular therapy; IPTW, inverse probability of treatment weighting; SMD, standardized mean difference. Values are presented as mean±standard deviation or n (%).

Table 2. Lesion and Procedural Data

Variables	Before IPTW				After IPTW		
	High-dose DCB (n=626)	Low-dose DCB (n=194)	*p* value	SMD	High-dose DCB (n=625.8)	Low-dose DCB (n=196.6)	SMD
Lesion length, mm	192.7±115.0	164.6±104.2	0.002	0.256	185.8±113.2	190.0±124.2	0.035
Lesion length ≥150 mm	306 (48.9)	89 (45.9)	0.516	0.060	291.3 (46.5)	103.6 (52.7)	0.123
Moderate/severe calcification	203 (32.4)	69 (35.6)	0.469	0.066	207.4 (33.1)	71.0 (36.1)	0.062
Total occlusion	293 (46.8)	79 (40.7)	0.160	0.123	283.3 (45.3)	84.0 (42.7)	0.051
No. of patent runoff vessels			0.994	0.023			0.096
0	13 (2.1)	4 (2.1)			12.8 (2.1)	4.7 (2.4)	
1	45 (7.2)	15 (7.7)			48.3 (7.7)	10.7 (5.4)	
2	95 (15.2)	30 (15.5)			95.2 (15.2)	29.0 (14.7)	
3	473 (75.6)	145 (74.7)			469.5 (75.0)	152.2 (77.4)	
Post-procedure ABI	0.88±0.15	0.89±0.11	0.587	0.048	0.88±0.15	0.88±0.12	0.001
Adjunctive atherectomy	143 (22.8)	32 (16.5)	0.074	0.160	141.7 (22.6)	36.8 (18.7)	0.097
Subintimal approach	85 (13.7)	21 (10.9)	0.382	0.084	83.2 (13.4)	25.2 (13.0)	0.013
TASC-II type			0.143	0.127			0.061
A or B	299 (47.8)	105 (54.1)			309.3 (49.4)	103.1 (52.5)	
C or D	327 (52.2)	89 (45.9)			316.5 (50.6)	93.5 (47.5)	
Lesion location			0.001	0.365			0.254
SFA	424 (67.7)	156 (80.4)			442.7 (70.7)	134.6 (68.4)	
SFA and PA	151 (24.1)	31 (16.0)			136.2 (21.7)	52.7 (26.8)	
PA only	51 (8.2)	7 (3.6)			46.9 (7.5)	9.2 (4.7)	
PA involvement	202 (32.3)	38 (19.6)	0.001	0.292	183.1 (29.3)	62.0 (31.5)	0.049
Provisional stenting	100 (16.0)	8 (4.1)	<0.001	0.402	96.2 (15.4)	8.5 (4.3)	0.376
Technical success	609 (97.3)	184 (94.8)	0.152	0.126	-	-	
Complications					-	-	
Vascular rupture	10 (1.6)	0 (0.0)	0.162		-	-	
Embolization	0 (0.0)	1 (0.5)	0.535		-	-	
Bleeding	9 (1.4)	4 (2.1)	0.780		-	-	
In-hospital death	2 (0.3)	0 (0.0)	>0.999		-	-	

ABI, ankle-brachial index; DCB, drug-coated balloon; IPTW, inverse probability of treatment weighting; PA, popliteal artery; SFA, superficial femoral artery; SMD, standardized mean difference; TASC, Trans-Atlantic Inter-Society Consensus.
Values are presented as mean±standard deviation or n (%).

Table 3. Risk of 12-Month Adverse Clinical Outcomes according to DCB Paclitaxel Dose

Outcome	DCB	No.	Before IPTW		After IPTW	
			Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Target lesion revascularization	High-dose	626	1.0 (reference)		1.0 (reference)	
	Low-dose	194	1.42 (0.87–2.32)	0.163	1.33 (0.73–2.42)	0.353
Major adverse limb event	High-dose	626	1.0 (reference)		1.0 (reference)	
	Low-dose	194	1.38 (0.85–2.23)	0.187	1.26 (0.70–2.27)	0.434
All-cause mortality	High-dose	626	1.0 (reference)		1.0 (reference)	
	Low-dose	194	0.70 (0.36–1.36)	0.294	0.67 (0.30–1.46)	0.311

CI, confidence interval; DCB, drug-coated balloon; HR, hazard ratio; IPTW, inverse probability of treatment weighting.
HRs are based on fully adjusted Cox proportional hazard models for factors associated with the specified outcomes.

was not associated with an increased risk of clinically driven TLR on multivariable analysis. Chronic heart failure and chronic kidney disease were the only independent predictors of clinically driven TLR after DCB treatment.

DISCUSSION

In this multicenter cohort study, EVT of FPA disease with DCBs demonstrated generally favorable 12-month clinical outcomes in terms of freedom from clinically driven TLR and MALE.

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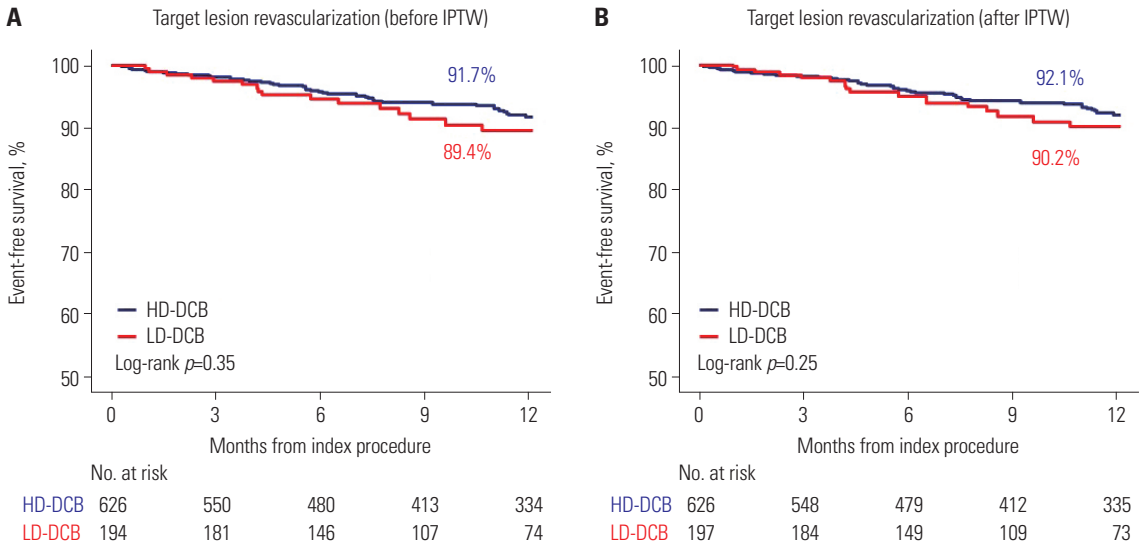

Fig. 2. Primary outcome before and after inverse probability of treatment weighting. Target lesion revascularization before IPTW (A) and after IPTW (B). DCB, drug-coated balloon; HD, high-dose; IPTW, inverse probability of treatment weighting; LD, low-dose.

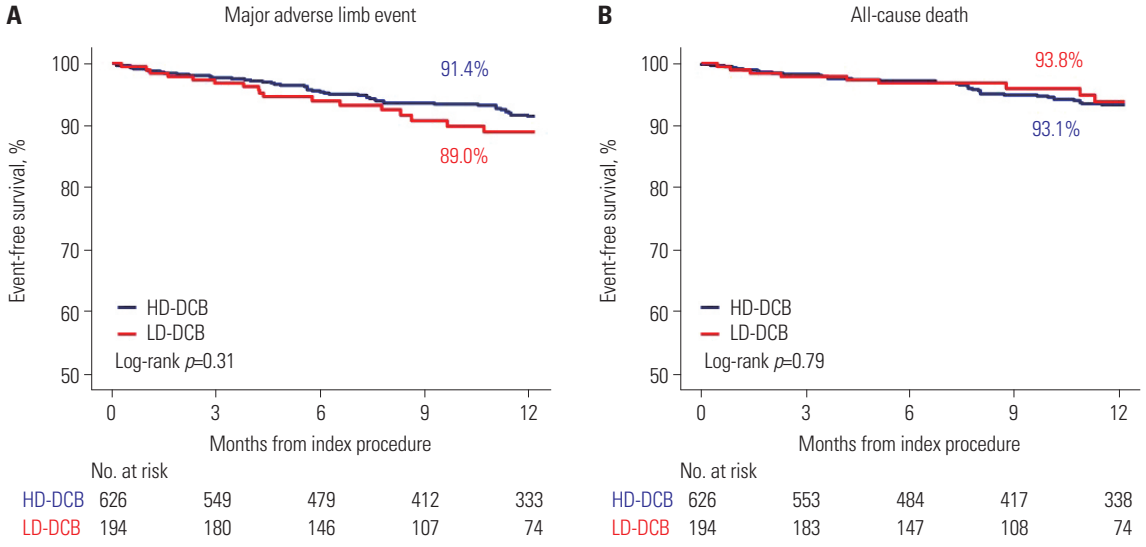

Fig. 3. Secondary outcomes. Major adverse limb event (A) and all-cause death (B). DCB, drug-coated balloon; HD, high-dose; LD, low-dose.

Furthermore, we found no significant differences in efficacy or safety between a high-dose paclitaxel DCB and two low-dose paclitaxel DCBs.

DCBs have been developed to reduce the likelihood of restenosis after angioplasty for peripheral or coronary artery disease. In general, DCBs consist of three main components: a balloon platform, an antiproliferative drug, and an excipient (which binds the antiproliferative drug to the balloon). Paclitaxel is the most commonly utilized antiproliferative drug in DCBs due to its high lipophilicity, which promotes rapid absorption through cell membranes. Paclitaxel inhibits neointimal smooth muscle cell proliferation to prevent restenosis. Hydrophilic excipients facilitate dissolution of paclitaxel and its transport into vascular tissues.[21-23]

Several paclitaxel-coated balloons with different formulations are currently available for EVT of FPA disease in Korea. The IN.PACT DCB consists of 3.5 μg/mm^2 paclitaxel and urea (a hydrophilic excipient), whereas the Lutonix DCB is formulated with 2.0 μg/mm^2 paclitaxel, polysorbate (an amphiphilic excipient), and sorbitol, and the Ranger DCB contains 2.0 μg/mm^2 paclitaxel and acetyltributyl citrate (a hydrophobic excipient). All three DCBs have been reported to produce excellent mid-term clinical outcomes when used to treat FPA.

Only a limited number of clinical studies have directly compared individual DCB devices in patients with FPA disease. In the COMPARE trial, a multicenter, randomized controlled study, no significant difference in 12-month primary patency or freedom from clinically driven TLR was observed between a high-dose DCB (IN.PACT) and low-dose DCB (Ranger). Similarly, IN.PACT and the Passeo-18 Lux DCB (3.0 μg/mm^2 paclitaxel+

Table 4. Predictors of Clinically Driven Target Lesion Revascularization after DCB Treatment

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Type of DCB				
Low-dose (vs. high-dose)	1.28 (0.71–2.33)	0.414	1.33 (0.73–2.42)	0.353
Lutonix (vs. IN.PACT)	1.46 (0.72–2.97)	0.291		
Ranger (vs. IN.PACT)	1.03 (0.41–2.57)	0.947		
Age	0.99 (0.97–1.02)	0.533		
Male sex	0.66 (0.36–1.21)	0.180		
Body mass index	0.96 (0.89–1.04)	0.291		
Hypertension	1.25 (0.66–2.38)	0.493		
Chronic heart failure	3.80 (1.73–8.36)	<0.001	3.23 (1.40–7.42)	0.006
CKD	2.46 (1.45–4.18)	<0.001	1.81 (1.01–3.27)	0.048
Diabetes mellitus	1.01 (0.58-1.77)	0.973		
Previous EVT	1.78 (1.05–3.02)	0.032	1.57 (0.89–2.75)	0.116
Previous amputation	2.10 (0.96-4.57)	0.062	1.17 (0.48–2.86)	0.737
Adjunctive atherectomy	0.95 (0.50–1.83)	0.887		
Pre-procedural ABI <0.7	1.60 (0.82–3.11)	0.165		
CLTI	2.05 (1.21–3.47)	0.008	1.65 (0.95–2.84)	0.074
Popliteal artery involvement	1.76 (1.03–3.01)	0.038	1.66 (0.96–2.86)	0.068
Moderate/severe calcification	0.81 (0.45–1.44)	0.472		
Total occlusion	0.82 (0.48–1.41)	0.480		
Lesion length ≥150 mm	1.29 (0.76–2.19)	0.344		

ABI, ankle-brachial index; CI, confidence interval; CKD, chronic kidney disease; CLTI, chronic limb-threatening ischemia; DCB, drug-coated balloon; EVT, endovascular therapy; HR, hazard ratio.

butyryl trihexyl citrate as excipient) exhibited comparable rates of freedom from clinically driven TLR in the BIOPACT study.[24] Safety endpoints also did not differ between DCBs in these studies. Some large cohort comparative studies have included more complex lesions. The PROSPECT MONSER study compared IN.PACT and Ranger in a propensity score–matched study population and found similar primary patency rates (81.3% vs. 87.0%) and clinically driven TLR rates (90.1% vs. 93.0%) between the types of DCB. In contrast to our study results, the POPCORN registry study found higher rates of 1-year primary patency (86.2% vs. 73.3%) and TLR-free survival (92.5% vs. 84.9%) with the IN.PACT DCB than with the Lutonix DCB in a propensity score–matched study population. Additionally, two global single-arm registry studies reported 2-year outcomes of IN.PACT and Lutonix DCBs.[25,26] Freedom from clinically driven TLR was 92.8% at 12 months and 83.5% at 24 months for lesions 12.1±9.5 cm in length in the IN.PACT registry, whereas TLR-free survival was 93.4% at 12 months and 89.3% at 24 months for lesions 10.1±8.4 cm in length in the Lutonix registry. Based on these two cohort studies, IN.PACT and Lutonix DCBs appear to be similarly effective in treating FPA lesions.

However, when comparing the baseline clinical and lesion characteristics as well as the procedural data, there are both similarities and differences between the studies. Target lesions were similarly long in our study and the PROSPECT MONSERT registry study (approximately 180 mm), while the lesions were shorter (approximately 135 mm) in the POPCORN registry study. Whereas our study evaluated only native vessel lesions, the PROSPECT MONSTER and POPCORN studies included in-stent restenosis lesions (in 13% and 18% of limbs, respectively). These two Japanese registry studies also included a higher percentage of patients receiving dialysis (29%–35%) than in our cohort (17%) and a lower proportion of limbs treated with provisional stenting (3%–5%). Additionally, intravascular ultrasonography (IVUS) was used in approximately 70% of procedures in these two studies. Although data regarding IVUS use were not available in our registry, IVUS is used very infrequently in Korea since it is not reimbursed by the national insurance system. Furthermore, Lutonix and Ranger were grouped together as low-dose DCBs in our study, whereas previous registry studies compared individual DCBs. Due to the heterogeneity in study design and the clinical and lesion characteristics of study participants, the results of previous DCB studies cannot be directly compared with each other or with our findings. Additionally, all clinical studies, except for the COMPARE trial, were non-randomized, which introduced potential bias despite statistical adjustments. We need to consider that our study population treated with either Lutonix or Ranger was smaller than that of the POPCORN study. Additionally, we report freedom from clinical driven TLR rather than primary patency, as reported in the POPCORN study. However, except for the POP-

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CORN study, all other investigations demonstrated similar clinical outcomes between high-dose and low-dose paclitaxel-coated balloons. Since DCBs consist of not only paclitaxel but also excipients and a balloon platform, their efficacy in reducing restenosis may not depend solely on the paclitaxel dose. However, it is challenging to assess the clinical efficacy of the excipients or other components in each DCB separately from the DCB as a whole. Based on the present study and the majority of previous studies, the three DCBs appear to be similarly effective.

The safety of paclitaxel-eluting devices has been the subject of recent debate. Katsanos, et al.[27] reported increased mortality following the use of paclitaxel-coated balloons and stents in the FPA in a meta-analysis of randomized trials. However, patient-level data from the clinical studies included in the Katsanos analysis, as well as more recent meta-analyses, have not confirmed a link between paclitaxel-coated devices and increased mortality.[28] In July 2023, the U.S. Food and Drug Administration declared that there was no association between paclitaxel-coated devices and late mortality risk.[29] Katsanos, et al.[30] also identified a significant dose-dependent association between paclitaxel exposure and the risk of major amputation. In our previous K-VIS ELLA registry study, we found no apparent relationship between the use of DCBs or drug-eluting stent, compared with BMS, and the risk of mortality or amputations.[5] Furthermore, within the limits of the present study, no dose-related risk of mortality or amputation was detected.

This study had several limitations. Firstly, it was not a randomized trial designed to evaluate the efficacy of high-dose DCB versus low-dose DCB. Instead, it was an observational cohort study, which can introduce selection bias, although we used IPTW to adjust for confounding factors. Secondly, we combined limbs treated with Lutonix or Ranger to create the low-dose DCB group due to the relatively small number of limbs treated with these DCBs. However, the patients and limbs treated with these DCBs exhibited similar baseline characteristics and clinical outcomes. Thirdly, participants were not routinely followed with imaging tests, preventing us from analyzing primary vessel patency data (which would provide more objective evidence of DCB efficacy than our clinically based outcomes). Nevertheless, this study reflected real-world clinical practice. Lastly, the follow-up duration was shorter for limbs treated with the Ranger DCB than for other DCBs as it only recently became available. This limited our follow-up duration to 1 year.

In conclusion, this real-world cohort study of patients with complex FPA disease demonstrated similar 12-month clinical outcomes in terms of freedom from clinically driven TLR, freedom from MALE, and freedom from all-cause mortality between limbs treated with high-dose paclitaxel DCB versus low-dose paclitaxel DCB.

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