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# Safety and Effectiveness of Passeo-18 Lux Drug-Coated Balloon Catheter in Infrainguinal Endovascular Revascularization in the Korean Population: A Multicenter Post-Market Surveillance Study

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**Objective:** To evaluate the safety and clinical outcomes of the Passeo-18 Lux drug-coated balloon (DCB) in endovascular revascularization procedures under real-world conditions in a Korean population with atherosclerotic disease of the infrainguinal arteries, including below-the-knee (BTK) arteries.

**Materials and Methods:** Eight institutions in the Republic of Korea participated in this prospective, multicenter, single-arm, post-market surveillance study. Two hundred patients with Rutherford class 2–5 peripheral arterial disease and infrainguinal lesions suitable for endovascular treatment were competitively enrolled. Data were collected at baseline, the time of intervention, discharge, and 1-, 6-, 12-, and 24-month follow-up visits. The primary safety endpoint was freedom from major adverse events (MAE) within 6 months (except when limiting the time frame for procedure- or device-related mortality to within 30 days), and the primary effectiveness endpoint was freedom from clinically driven target lesion revascularization (CD-TLR) within 12 months after the procedure.

**Results:** A total of 197 patients with 332 target lesions were analyzed. Two-thirds of the patients had diabetes mellitus, and 41.6% had chronic limb-threatening ischemia. The median target lesion length was 100 mm (interquartile range: 56–133 mm). Of the target lesions, 35.2% were occlusions, and 14.8% were located in the BTK arteries. Rate of freedom from MAE was 97.9% at 6 months, and the rate of freedom from CD-TLR was 95.0% and 92.2% at 12 and 24 months, respectively. Subgroup analysis of 43 patients and 49 target lesions involving the BTK arteries showed rate of freedom from MAE of 92.8% at 6 months and rates of freedom from CD-TLR of 88.8% and 84.4% at 12 and 24 months, respectively.

**Conclusion:** The results of the present study, including the BTK subgroup analysis, showed outcomes comparable to those of other DCB studies, confirming the safety and effectiveness of Passeo-18 Lux DCB in the Korean population.

**Keywords:** Peripheral artery disease; Drug-coated balloon; Korean; Below-the-knee

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## INTRODUCTION

Peripheral artery disease (PAD) of the lower extremities is a common condition affecting over 200 million people globally, which is rapidly increasing in prevalence [1,2]. Decreased blood flow to the leg in patients with PAD can cause symptoms ranging from intermittent claudication to chronic limb-threatening ischemia (CLTI), defined as ischemic rest pain, ischemic foot ulceration, or gangrene [3,4]. In patients with PAD and CLTI, the major amputation rate can reach as high as 22% at the 1-year follow-up if revascularization cannot be performed [5]. In Korea, the prevalence of PAD was 4.6% between 2008 and 2012, and is expected to increase as the country continues to become an increasingly aging society [6,7].

Endovascular revascularization is increasingly being used in patients with PAD as endovascular devices and techniques have advanced. Drug-coated balloons (DCB) are endovascular devices in which antiproliferative drugs, such as paclitaxel, are used to coat the surface of the balloon catheter. These antiproliferative drugs are delivered to the vessel wall during balloon inflation, inhibiting neointimal hyperplasia of the vessel wall [8,9]. Several randomized controlled trials (RCTs) have previously demonstrated that DCBs provide better outcomes than plain balloons in femoropopliteal arteries [10-17]. However, previous studies comparing DCB and plain balloon angioplasty for below-the-knee (BTK) artery disease have reported mixed results, requiring further investigation to establish the role of DCB in the treatment of BTK artery disease [18-20].

The Passeo-18 Lux (Biotronik AG, Buelach, Switzerland) is a DCB made by coating paclitaxel 3 μg/mm$^2$ on the surface of the Passeo-18 plain balloon catheter (Biotronik AG) using butyryl-tri-n-hexyl citrate (BTHC) as an excipient. Compared with the uncoated Passeo-18 balloon, the Passeo-18 Lux DCB showed superior outcomes for femoropopliteal lesions in the BIOLUX P-I RCT [10], and comparable outcomes for infrapopliteal lesions in the BIOLUX P-II RCT [21]. In addition, the BIOLUX P-III study, a single-arm, prospective, international, multicenter, post-market study operating an all-comers registry, reported 24-month outcomes of Passeo-18 Lux DCB in a large population in real-world clinical practice [22].

Several previous studies have reported that, in patients with PAD, ethnic differences may be associated with differences in the prevalence and severity of the disease, prognosis after endovascular therapy, and amputation rate [23-26]. However, only a few studies have reported on the outcomes of DCB in Asian populations. Therefore, this single-arm, prospective, multicenter, post-market surveillance study aimed to evaluate the safety and clinical outcomes of the Passeo-18 Lux DCB in endovascular revascularization procedures in a Korean population with atherosclerotic disease of the infrainguinal arteries, including the BTK arteries, under real-world conditions.

## MATERIALS AND METHODS

### Study Population

Eight institutions in the Republic of Korea participated in this study, competitively enrolling 200 patients. The Institutional Review Board of each participating institution approved the study protocol. The Institutional Review Board of each participating institution approved the study protocol (IRB No. AJOUIRB-DEV-2017-478). Written informed consent was obtained from all patients before enrollment. This study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization of Good Clinical Practices, and the applicable laws of the Republic of Korea. The results of the present study are reported in accordance with the guidelines of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity PAD [27].

Patients were eligible if they were 19 years or older, had Rutherford class 2–5 peripheral arterial disease, had infrainguinal lesions suitable for endovascular treatment using Passeo-18 Lux DCB, or had at least one patent outflow vessel without significant stenosis (> 50%) of the foot. We excluded patients with a life expectancy of < 1 year, acute thrombosis, history of bypass surgery, planned major amputation, or failure to cross the target lesion with a guidewire.

### Study Device

Passeo-18 Lux DCB was CE-marked in Europe in January 2014, and approved for clinical use by the Ministry of Food and Drug Safety of the Republic of Korea in July 2016. The surface of the balloon is homogenously coated with paclitaxel (3 μg/mm$^2$) incorporated in the excipient BTHC. The available balloon sizes were 2.0–7.0 mm in diameter and 40 and 120 mm in length.

### Endovascular Procedure

After successfully passing the guidewire through the


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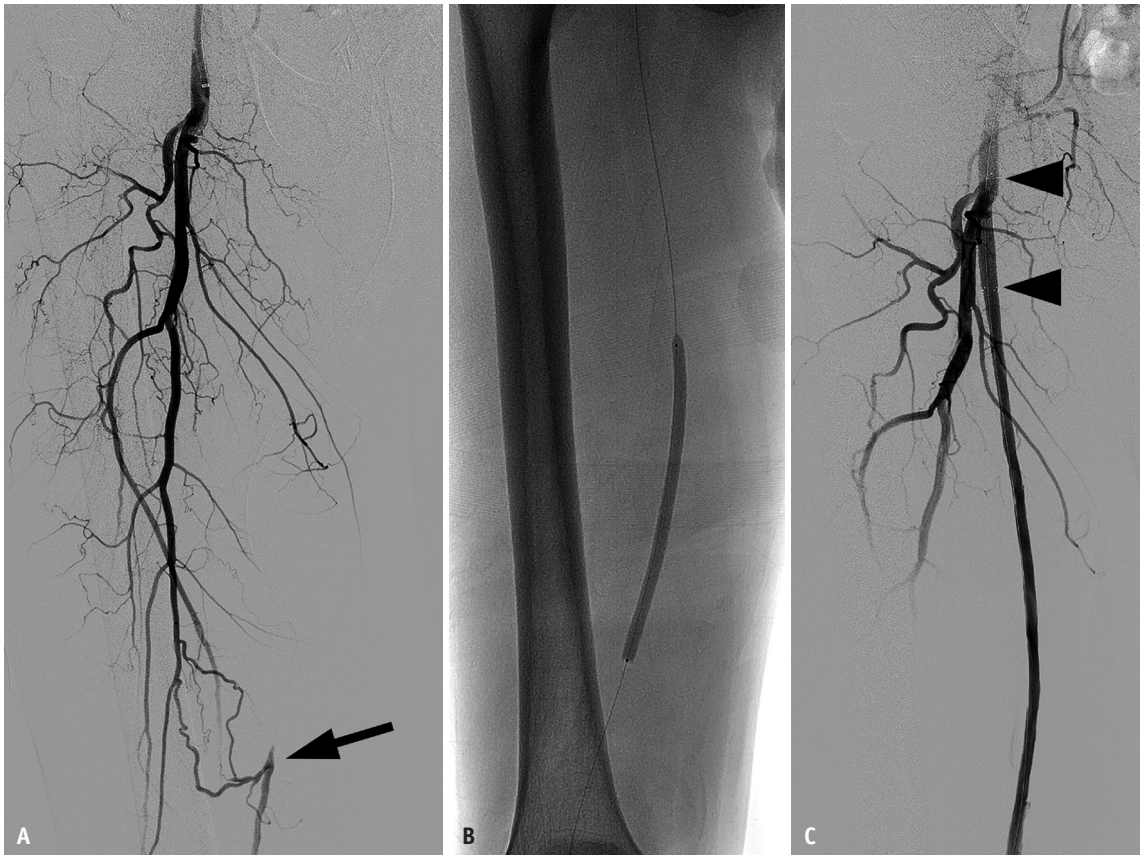


**Fig. 1.** A 76-year-old man with claudication. **A:** Common femoral angiogram showing a long-segmental occlusion of the right superficial femoral artery and reconstitution of the flow in the distal part (arrow) through collaterals from the deep femoral artery. After successful guidewire passage and pre-dilatation, Passeo-18 Lux drug-coated balloon catheters were applied. **B:** Fluoroscopy image showing a drug-coated balloon of 5 mm in diameter and 12 cm in length inflated in the lesion. **C:** Final angiography showing good arterial flow without residual stenosis after provisional stenting (arrowheads) due to elastic recoil.

target lesion, a DCB was applied to cover the target lesion and the 10 mm proximal and distal margins (Fig. 1). The DCB inflation time was 180 seconds. When multiple DCBs were required to cover a long target lesion, they were applied to maintain a minimum overlap length of 10 mm, and to minimize geographically missed areas. Pre and postdilatation using a plain balloon catheter and adjunctive endovascular devices, including bare-metal stents and atherectomy, were not limited to this study, and were applied according to the standard clinical practice of the operator.

### Data Collection and Follow-Up

Data were collected at baseline, time of intervention, discharge, and at the 30 ± 14-day and 6 ± 1, 12 ± 1, and 24 ± 1-month follow-up visits routinely conducted after the procedure. The investigator visually assessed the angiography images and determined lesion characteristics, including lesion length, location, reference vessel diameter, degree of stenosis, and calcification. If several short segmental lesions could be treated with one DCB, these were defined as one "treatment segment."

### Endpoints

The primary safety endpoint was assessed based on freedom from major adverse events (MAEs) within specified timeframes. MAE was defined as any procedure- or device-related mortality, major target limb amputation, or clinically driven target lesion revascularization (CD-TLR). The assessment of the primary safety endpoints specifically considered these events within a 6-month time frame, except for mortality, which was limited to within 30 days. The primary endpoint of effectiveness was freedom from CD-TLR within 12 months of the procedure. CD-TLR analysis was performed based on the lesions.

The secondary endpoints were device success, technical

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success, procedural success, freedom from CD-TLR within 24 months, and amputation-free survival (with target limb amputation and all-cause mortality included as events) and all-cause mortality within 6, 12, and 24 months. Device success was defined as successful delivery, inflation, deflation, and retrieval of the study devices, and was analyzed on a per-device basis. Technical success was defined as completion of the index procedure, with residual stenosis ≤ 30% of the target lesion on final angiography. Technical success was analyzed on a per-lesion basis. Procedural success was defined as device and technical success without MAE during the hospital stay and was analyzed per patient.

### BTK Subgroup Analysis

Patients with at least one lesion involving the BTK arteries and those with lesions involving the BTK arteries treated with the study device were analyzed separately to evaluate the outcomes of the Passeo-18 Lux DCB for BTK artery lesions.

### Statistical Analysis

Categorical data are presented as percentages of the total number. After performing the Shapiro–Wilk test, continuous data following normal distribution were presented as the mean ± standard deviation (range), or as the median (interquartile range) if they did not fulfill this criterion. Clinical outcomes, including rate of freedom from MAE, CD-TLR, and amputation-free survival, were calculated using the Kaplan–Meier method. Statistical analyses were performed using SPSS (version 25.0, IBM Corp., Armonk, NY, USA) and R software (version 4.3.2, R Foundation for Statistical Computing; https://www.r-project.org).

**Table 1.** Patients' characteristics

| | Full cohort (n = 197) | BTK subgroup (n = 43) |
|---|---|---|
| Age, yr | 70 ± 9 [42–92] | 70 ± 10 [42–87] |
| Sex, male | 165 (83.8) | 33 (76.7) |
| Diabetes mellitus | 130 (66.0) | 32 (74.4) |
| Insulin-dependent | 2 (1.0) | 0 (0.0) |
| Cigarette smoking | 53 (26.9) | 14 (32.6) |
| Current smoker | 32 (16.2) | 9 (20.9) |
| Dyslipidemia | 17 (8.6) | 5 (11.6) |
| Hypertension | 136 (69.0) | 28 (65.1) |
| Coronary artery disease | 64 (32.5) | 9 (20.9) |
| Cerebrovascular disease | 8 (4.1) | 4 (9.3) |
| Renal disease | 52 (26.4) | 15 (34.9) |
| Previous peripheral intervention | 18 (9.1) | 3 (7.0) |
| Rutherford classification | | |
| 2 | 52 (26.4) | 6 (14.0) |
| 3 | 63 (32.0) | 5 (11.6) |
| 4 | 30 (15.2) | 7 (16.3) |
| 5 | 52 (26.4) | 25 (58.1) |
| BTK artery lesion | 43 (21.8) | 43 (100.0) |

Data are presented as the mean ± standard deviation [range] and categorical data are presented as number (%).
BTK = below-the-knee

## RESULTS

### Patient and Lesion Characteristics

A total of 200 patients were initially enrolled at eight centers in the Republic of Korea between April 2018 and February 2020 (Supplementary Table 1, Supplementary Fig. 1). Three patients withdrew before the procedure, and

**Table 2.** Lesion characteristics

| | Full cohort (n = 332) | BTK subgroup (n = 49) |
|---|---|---|
| Target lesion length, mm | 100 [56–133] | 90 [45–112] |
| Reference vessel diameter, mm | 5.0 [4.0–6.0] | 2.5 [2.3–3.0] |
| Target lesion stenosis, % | 90 [70–100] | 99 [90–100] |
| Occlusion | 117 (35.2) | 23 (46.9) |
| Lesion type | | |
| De novo | 309 (93.1) | 46 (93.9) |
| Restenosis without stent | 10 (3.0) | 3 (6.1) |
| In-stent restenosis | 13 (3.9) | 0 (0.0) |
| Calcification | | |
| None | 55 (16.6) | 12 (24.5) |
| Mild | 92 (27.7) | 16 (32.7) |
| Moderate | 92 (27.7) | 12 (24.5) |
| Severe | 93 (28.0) | 9 (18.4) |
| Target lesion location* | | |
| Superficial femoral artery | 229 (69.0) | 2 (4.1) |
| Popliteal artery | 89 (26.8) | 6 (12.2) |
| Tibioperonal trunk | 20 (6.0) | 20 (40.8) |
| Anterior tibial artery | 15 (4.5) | 15 (30.6) |
| Posterior tibial artery | 14 (4.2) | 14 (28.6) |
| Peroneal artery | 9 (2.7) | 9 (18.4) |
| BTK artery lesion | 49 (14.8) | 49 (100.0) |

Data are presented as the median [interquartile range] and categorical data are presented as number (%).
*If the target lesion involves more than one anatomical segment in the table, it was counted for every involved segment (e.g., a long lesion involving superficial femoral and popliteal arteries was counted twice: one for the superficial femoral artery and the other for the popliteal artery).
BTK = below-the-knee


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197 patients with 332 target lesions were analyzed.

Tables 1 and 2 show the baseline characteristics of the study patients and the target lesions, respectively. The mean age of the patients was 70 ± 9 years (range: 42–92 years), and 83.8% were male. Two-thirds of the patients had diabetes mellitus, 26.9% were current or previous smokers, and 41.6% had CLTI (Rutherford class > 3). Of 332 target lesions, 93.1% were de novo. The median target lesion length was 100 mm (interquartile range: 56–133 mm). Approximately 35.2% of the patients had occluded segments and 14.8% had lesions in the BTK arteries.

### Procedure Characteristics and Outcomes

Table 3 summarizes the details of the study procedure. Among the 332 target lesions, 17.2% underwent atherectomy before DCB and 13.3% required provisional stenting after DCB. The device, technical, and procedural success rates were 100.0% (457/457), 98.2% (326/332), and 96.4% (190/197), respectively.

Table 4 and Figures 2 and 3 show the clinical outcomes of Passeo-18 Lux DCB. The rate of freedom from MAE at 6 months, which was the primary safety endpoint, was 97.9% (Fig. 2). No procedural- or device-related mortality occurred within 30 days of the index procedure. Rate of freedom from CD-TLR at 12 months, the primary effectiveness endpoint, was 95.0% falling slightly to 92.2% at 24 months (Fig. 3).

The all-cause mortality rates were 3.1%, 5.9%, and 14.8% at 6, 12, and 24 months, respectively. The median interval between the procedure and death among those who died (n = 22) was 358 days (range, 14–680 days). Among them, three mortalities occurred within 30 days of the index procedure unrelated to the procedure or device (i.e., non-MAE), with the primary causes of death being sepsis (interval: 26 days), aggravation of the underlying disease (interval: 21 days), and pneumonia (interval: 14 days). Two cases of amputation were noted during the follow-up period: one patient underwent below-ankle amputation 690 days after the procedure, whereas the other underwent above-knee amputation 416 days after the procedure. These amputations were caused by the aggravation of the underlying PAD and were not considered to be related to the procedure or device.

### BTK Subgroup Analysis

The present study included 43 patients with at least one lesion involving the BTK arteries among 197 patients, and 49 lesions involving the BTK arteries among 332 lesions. Subgroups of 43 patients and 49 lesions were analyzed separately to evaluate the outcomes of Passeo-18 Lux DCB for BTK arterial lesions.

Among the 43 patients, 74.4% had diabetes mellitus and 74.4% had CLTI (16.3% with Rutherford class 4 and 58.1% with class 5) (Table 1). Among the 49 lesions, 46.9% were occluded, and the median target lesion length was 90 mm (interquartile range: 45–112 mm) (Table 2). Device, technical,

**Table 3.** Procedure details

| | Full cohort | BTK subgroup |
|---|---|---|
| Procedure time, min | 82 [59–111] | 80 [61–108] |
| Fluoroscopy time, min | 19 [13–31] | 17 [13–33] |
| Atherectomy prior to DCB | 57 (17.2) | 0 (0.0) |
| Pre-dilatation | 287 (86.4) | 41 (83.7) |
| Dissection | 19 (5.7) | 2 (4.1) |
| Post-dilatation | 25 (7.5) | 7 (14.3) |
| Provisional stenting | 44 (13.3) | 3 (6.1) |
| Procedure outcome | | |
| Device success | 457 (100.0) | 62 (100.0) |
| Technical success | 326 (98.2) | 49 (100.0) |
| Procedural success | 190 (96.4) | 42 (97.7) |

Data are presented as the median [interquartile range] and categorical data are presented as number (%).
BTK = below-the-knee, DCB = drug-coated balloon, Device success = the successful delivery, inflation, deflation, and retrieval of the study devices, Technical success = the completion of the index procedure with residual stenosis ≤ 30% on angiography, Procedural success = device and technical success without developing major adverse events during the hospital stay

**Table 4.** Clinical outcomes

| Outcome | Follow-up time (month) | Full cohort | BTK subgroup |
|---|---|---|---|
| MAE | 6 | 2.1 (0.0–4.2) | 7.2 (0.0–14.8) |
| | 12 | 5.0 (1.7–8.1) | 9.9 (0.2–18.6) |
| | 24 | 9.7 (4.5–14.5) | 14.9 (0.9–26.9) |
| CD-TLR | 6 | 1.6 (0.2–2.9) | 6.4 (0.0–13.1) |
| | 12 | 5.0 (2.5–7.4) | 11.2 (1.4–20.0) |
| | 24 | 7.8 (4.3–11.2) | 15.6 (2.4–27.0) |
| Amputation | 6 | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) |
| | 12 | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) |
| | 24 | 2.0 (0.0–4.6) | 5.3 (0.0–14.8) |
| All-cause mortality | 6 | 3.1 (0.6–5.6) | 4.8 (0.0–11.1) |
| | 12 | 5.9 (2.4–9.2) | 7.4 (0.0–15.1) |
| | 24 | 14.8 (8.7–20.5) | 11.8 (0.0–22.5) |

Data are presented as the Kaplan–Meier estimates, i.e., cumulative incidence in percentage (95% confidence interval).
BTK = below-the-knee, MAE = major adverse event, CD-TLR = clinically driven target lesion revascularization


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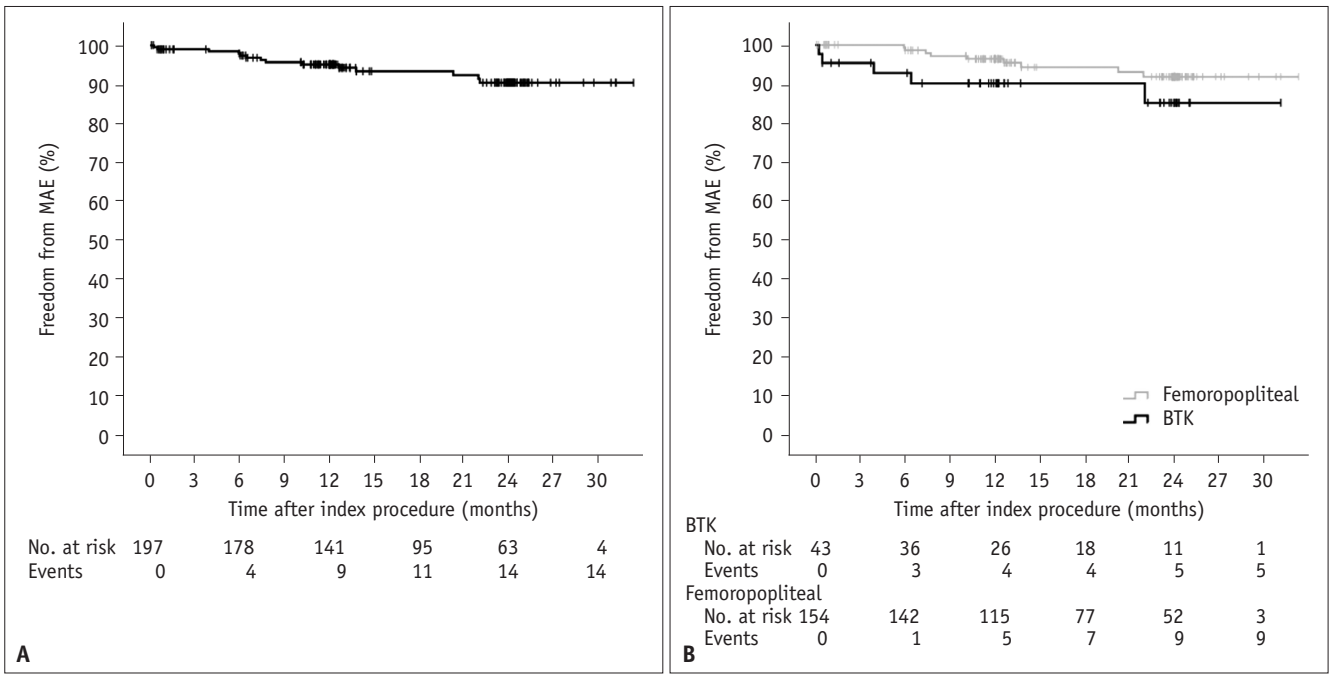


**Fig. 2.** Kaplan–Meier curve for rate of freedom from MAEs of the full cohort **(A)** and the BTK subgroup **(B)**. MAE = major adverse event, BTK = below-the-knee

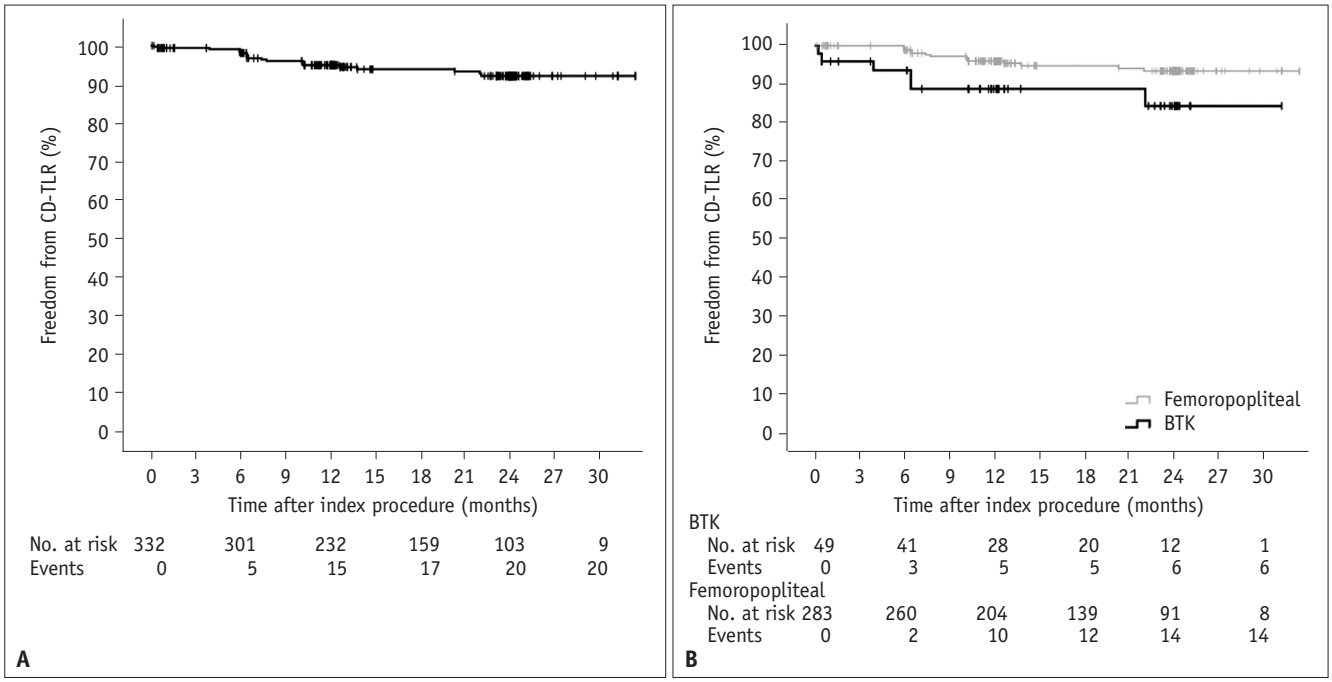


**Fig. 3.** Kaplan–Meier curve for rate of freedom from CD-TLR of the full cohort **(A)** and the BTK subgroup **(B)**. CD-TLR = clinically driven target lesion revascularization, BTK = below-the-knee

and procedural success rates were 100.0% (62/62), 100.0% (49/49), and 97.7% (42/43), respectively (Table 3). The rate of freedom from MAE was 92.8% at 6 months, and the rates of freedom from CD-TLR was 88.8% and 84.% at 12 and 24 months, respectively (Table 4, Figs. 2, 3).

## DISCUSSION

The present study was a prospective multicenter post-market surveillance study that evaluated the outcomes of the Passeo-18 Lux DCB in a Korean population. This study


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had minimal restrictions on the inclusion and exclusion criteria in order to reflect the real-world patient populations and clinical practices in Korea. Consequently, 41.6% of the study population had CLTI and 14.8% of the lesions were located in the BTK arteries.

The results of the present study are comparable to those of previous post-market surveillance studies that evaluated the DCB. In this study, the rate of freedom from MAE was 97.9% at 6 months, and the rates of freedom from CD-TLR were 95.0% and 92.2% at 12 and 24 months, respectively. The previous BIOLUX P-III registry, which was another post-market surveillance study of the Passeo-18 Lux DCB which included 42.1% CLTI patients and 17.0% BTK lesions, reported a rate of freedom from MAE of 94.5% at 6 months and rates of freedom from CD-TLR of 92.5% and 88.1% at 12 and 24 months, respectively [22]. Another post-market surveillance study of another DCB (SeQuent Please OTW; B. Braun, Melsungen, Germany), which included 46.7% CLTI patients and 8.0% BTK lesions, reported rate of freedom from all-cause TLR of 91.9% at 12 months [28].

Previous studies reported that ethnic differences are associated with differences in outcomes after endovascular treatment and amputation rates in patients with PAD [23-25]. In contrast to Western patients, Asian patients with CLTI are more likely to have multilevel disease with highly calcified long stenotic lesions [29]. In a propensity-matched study analyzing 1669 pairs of Asian and Caucasian patients, Asian patients presented with CLTI and underwent emergency intervention more frequently [24]. Additionally, Asian patients had significantly higher in-hospital mortality and worse primary patency after the intervention [24].

DCB is now considered one of the standard treatment modalities for femoropopliteal artery disease in the clinical practice guidelines [3,30]. However, only a few studies report on the outcomes of DCB in Asian populations with PAD, which may be considered a small study population [26,31-33]. IN.PACT PMS Japan was a post-market surveillance study conducted in Japan to evaluate the outcomes of IN.PACT Admiral (Medtronic, Dublin, Ireland) for femoropopliteal lesions, including 304 patients and 364 lesions [33]. IN.PACT PMS Japan reported a rate of freedom from an MAE of 91.0% at 6 months and rate of freedom from CD-TLR of 94.1% at 12 months. A subgroup analysis of the BIOLUX P-III registry reported that the Asian cohort (49 patients, 77 lesions) had higher rates of MAE, amputation, and mortality than the non-Asian cohort [26]. The rate of freedom from CD-TLR in the Asian cohort was 89.5% at 24 months [26]. An Asian subgroup analysis (114 patients, 138 lesions) of the IN.PACT global study to evaluate the outcomes of IN.PACT Admiral DCB in femoropopliteal artery disease reported freedom from CD-TLR rates of 95.3% and 92.1% at 12 and 24 months, respectively [31]. Although a recent BIOLUX P-IV China Study showed a higher CD-TLR of 98.6% at 12 months, this study only included patients with Rutherford class 2–4; most lesions were only present in the femoral artery (99.4%), and lesion lengths were relatively short (mean length of 74 mm) [34]. To the best of our knowledge, this is the second-largest prospective study evaluating the outcomes of DCB in an Asian population, second only to the IN.PACT PMS Japan study. Therefore, the results of our study may have significant implications in demonstrating the safety and effectiveness of DCB in Asian populations.

The BTK subgroup analysis revealed the outcomes of Passeo-18 Lux DCB in 43 patients with 49 lesions involving the BTK artery disease. The results of the previous BIOLUX P-II trial evaluating the outcome of Passeo-18 Lux DCB in BTK artery disease showed a low freedom from TLR of 69.9% at 12 months, which was not superior to that of the plain balloon [21]. The investigators of the BIOLUX P-II speculated that this high TLR rate may have been affected by the mandatory angiographic assessment performed at the 6-month follow-up [21]. The BTK subgroup analysis of the BIOLUX P-III registry, which included 151 patients and 185 lesions, showed a much higher freedom from CD-TLR of 90.9% at 12 and 24 months [35]. The results of the BTK subgroup in this study in terms of freedom from TLR at 12 months (88.8%) were comparable to those of the BIOLUX P-III (90.9%) and other studies on the outcome of DCB in BTK lesions, including the IN.PACT DEEP trial (88.1%) [36], APOLLO trial (90.6%) [37], and DEBATE-BTK trial (81.5%) [19]. However, further studies with larger study populations are required to confirm the safety and effectiveness of DCB in the treatment of BTK artery disease in Asian populations.

In the present study, the overall mortality rate was 14.8% at 24 months. Since the controversial meta-analysis by Katsanos et al. [38], several studies have reported an increased overall mortality in patients treated with paclitaxel [39,40]. However, a recent RCT [41] and other meta-analyses [42-45] showed no significant increase in overall mortality associated with paclitaxel. Although further evidence is required to settle this debate, the use of endovascular devices with paclitaxel can be decided by considering the risks and benefits to individual patients.

The present study has several limitations. First, this was

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a single-arm prospective study without a control group or randomization. As such, this study did not directly compare treatment modalities, endovascular devices, or patient populations. Secondly, this study did not include patients with Rutherford class 6 and did not analyze wound healing. Further studies are required in Asian populations with Rutherford class 6 PAD.

In conclusion, the results of the present study, including the BTK subgroup analysis, showed outcomes comparable to those of other DCB studies, confirming the safety and effectiveness of the Passeo-18 Lux DCB in the Korean population.

## Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2024.0099.

### Availability of Data and Material

The data are available from the corresponding author on reasonable request.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

### Author Contributions

Conceptualization: Je Hwan Won, Jinoo Kim. Data curation: all authors. Formal analysis: Tae Won Choi. Funding acquisition: Je Hwan Won. Investigation: all authors. Methodology: Tae Won Choi, Jinoo Kim. Project administration: Jinoo Kim. Resources: all authors. Supervision: Jinoo Kim, Je Hwan Won. Validation: Tae Won Choi. Visualization: Tae Won Choi. Writing—original draft: Tae Won Choi. Writing—review & editing: all authors.

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