Intravascular ultrasound predictors of restenosis after drug-coated balloon treatment for femoropopliteal artery: a post hoc analysis of IVUS-DCB trial

Lee, Jaeoh

Department of Medicine

Graduate School

Yonsei University

Intravascular ultrasound predictors of restenosis after drug-coated balloon treatment for femoropopliteal artery: a post hoc analysis of IVUS-DCB trial

Advisor Ko, Young-Guk

A Master's Thesis Submitted

to the Department of Medicine

and the Graduate School of Yonsei University

in partial fulfillment of the

requirements for the degree of

Master of Medical Science

Lee, Jaeoh

June 2025

Intravascular ultrasound predictors of restenosis after drug-coated balloon treatment for femoropopliteal artery: a post hoc analysis of IVUS-DCB trial

This Certifies that the Master's Thesis of Lee, Jaeoh is Approved

Committee Chair	**Min, Pil-Ki**
Committee Member	**Ko, Young-Guk**
Committee Member	**Joo, Hyun-Chel**

Department of Medicine
Graduate School
Yonsei University
June 2025

ACKNOWLEDGEMENTS

Firstly, I would like to express my deepest appreciation to my supervisor, Professor Young-Guk Ko. I would like to express my sincere gratitude for Dr.Ko's mentorship, not only as an academic advisor but also as a role model as a great cardiologist, and thank to him for encouraging me to pursue excellence in my work.

I am also thankful to the members of the thesis committee, Professor Pil-Ki Min and Hyun-Chel Joo, for their meticulous guidance on the areas where my research was lacking and for collaboratively exploring the objectives, limitations, and potential solutions to the challenges I faced

In addition, I am appreciating of Professor Myeong-Ki Hong, Professor Donghoon Choi, Professor Byeong-Keuk Kim, Professor Jung-Sun Kim, Professor Chul-Min Ahn, Professor Sung-Jin Hong, Professor Seung-Jun Lee, Professor Yong-Joon Lee, Professor Sang-Hyup Lee, and Professor In Tae Jin, who have supported me with substantial advice and encouragement, even during their busy schedules, helping me secure data and serving as excellent examples of dedicated researchers and great educators.

Finally, I am deeply grateful to my family members, for their support, understanding, and endless love for a busy husband and dad.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Intravascular ultrasound predictors for clinical or angiographic restenosis after drug-coated balloon treatment for femoropopliteal artery: a post hoc analysis of IVUS-DCB trial

Objectives: Intravascular ultrasound (IVUS) has been shown to improve outcomes of drug-coated balloon (DCB) angioplasty for treatment of femoropopliteal artery (FPA) disease. However, the optimal IVUS criteria for achieving improved outcomes of DCB angioplasty for FPA disease remain uncertain.

Methods: The study aimed to identify IVUS predictors for loss of patency at 12 months after DCB angioplasty for FPA disease. After excluding one patient due to insufficient IVUS imaging data, 98 patients in the IVUS-guidance group of the IVUS-DCB trial were included in the analysis. IVUS parameters predicting loss of patency at 12 months and their optimal cut-off values were investigated.

Results: Among the 98 patients who underwent IVUS-guided FPA intervention, 16 patients (16.3%) lost primary patency within 12 months. End-stage renal disease on hemodialysis and, bailout stenting, post-procedural dissection length >50% were independent procedural predictors for 12-month patency loss. Receiver operating characteristic (ROC) curve demonstrated that post-procedural minimal lumen area (MLA) $\geq$11.6 mm^2 (area under the ROC curve: 0.685, 95% CI: 0.513-0.857) as the optimal cut-off value for sustained primary patency. In survival analysis, patients with MLA $\geq$11.6 mm^2 had a hazard ratio of 0.27 (95% CI: 0.09-0.80, p-value =0.019, risk difference: 19.8) for lower risk of patency loss. A post-procedural MLA $\geq$11.6 mm^2 was an independent IVUS predictor of sustained primary patency after DCB angioplasty in patients with FPA disease.

Conclusions: Our findings suggest that lesion optimization and achieving sufficient lumen area under IVUS guidance during DCB angioplasty are crucial for maintaining target vessel patency.

Key words : Femoropopliteal artery, drug-coated balloon, intravascular ultrasound

1. INTRODUCTION

The femoropopliteal artery (FPA) is frequently affected in patients with atherosclerotic lower extremity artery disease. However, this site presents a challenging target for endovascular therapy (EVT) due to the typically long, occlusive, and calcified nature of FPA lesions[1, 2]. Moreover, although treatment with paclitaxel-releasing drug-coated balloons (DCBs) have shown to yield excellent clinical outcomes for patients these lesions, efficacy can be hindered by several complications, including dissection, recoil, and residual stenosis[3-8]. Consequently, careful optimization of target lesions before and after DCB treatment is essential for maintaining patency.

At present, angiography is the primary imaging modality for EVT; its two-dimensional imaging for the vessel lumen has limitation in assessing vessel dimensions and status during procedures. In contrast, intravascular ultrasound (IVUS), a catheter-based imaging tool, provides cross-sectional images of the vessel wall, enabling precise measurements of vessel dimensions and plaque characterization[9]. The clinical benefits of IVUS guidance for coronary artery intervention have been demonstrated in multiple trials[10-12], however, its utility for peripheral artery interventions remains less established[13].

Results from the IVUS-DCB trial (NCT 03517904) revealed that IVUS-guided DCB angioplasty for FPA lesions significantly improved primary patency at 1-year post-procedure and reduced the need for clinically driven target lesion revascularization compared to angiography-guided DCB angioplasty[14]. However, despite these findings, the optimal IVUS parameters associated with enhanced primary patency after DCB angioplasty for treatment of FPA lesions are not well defined. To address this question, in the present study, we aimed to identify IVUS parameters that can predict restenosis in the FPA following DCB angioplasty at 12-month follow-up.

2. METHODS

2.1. Study design and population

The IVUS-DCB trial was a multi-center randomized, controlled clinical trial included 243 patients with peripheral artery disease (PAD) from seven centers in South Korea. Symptomatic PAD patients ≥19 years of age with claudication (Rutherford classification 2 or 3) or critical limb-threatening ischemia (Rutherford classification 4 or 5) and >50% FPA stenosis confirmed were enrolled in the trial and provided written informed consent. Detailed study inclusion and exclusion criteria are described in Appendix 1. The study protocol received approval from the institutional review board at each participating center and was conducted in accordance with the principles of the Declaration of Helsinki. The IVUS-DCB trial registered at ClinicalTrials.gov (NCT 03517904).

In total, 119 individuals in the original trial were randomized to receive IVUS-guided angioplasty and completed the protocol. Of these individuals, 98 patients with imaging data available to assess binary restenosis at one year were included in our analysis, after excluding one patient who ultimately received angioplasty-guided intervention (Figure 1).

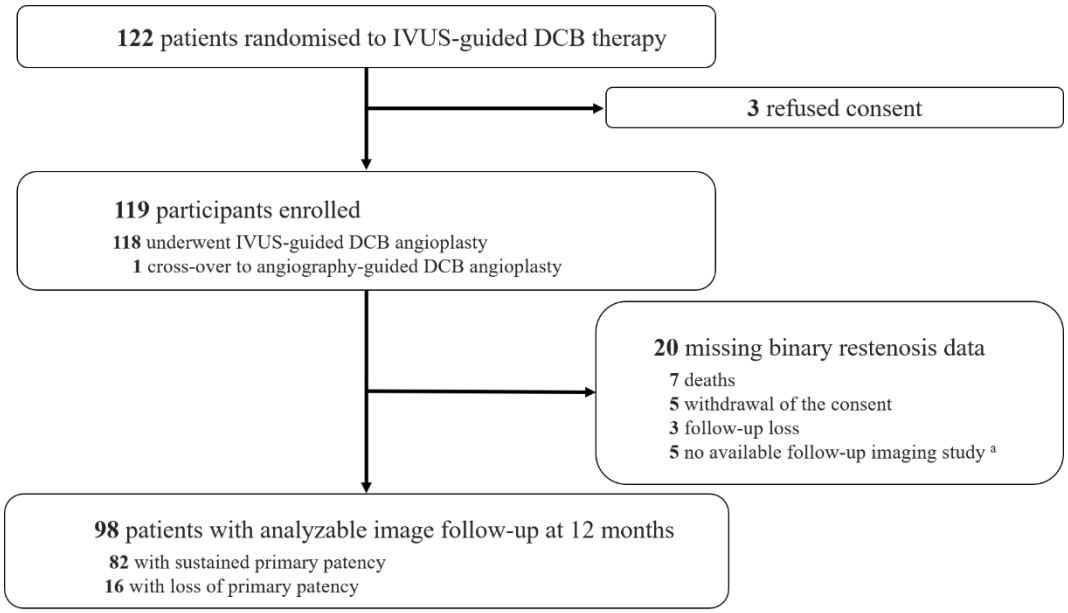


Figure 1. Flow chart summarizing the current study

[a] Patients with no available imaging data to evaluate binary restenosis at 12 months post-procedure.

Abbreviations: IVUS, Intravascular ultrasonography; DCB, Drug-coated balloon; FPA, Femoropopliteal artery

2.2. Procedures

IVUS evaluation were performed at least twice: once before and once after DCB angioplasty, upon the completion of the procedure. The Volcano s5 IVUS system (Phillips Healthcare, Andover, MA, USA) was used with 74 patients, and the Boston Scientific iLab2 IVUS system (Boston Scientific, Marlborough, MA, USA) was used with 24 patients. All imaging operators were interventional cardiologists experienced in the use of IVUS for both coronary and peripheral artery interventions.

Both contralateral and ipsilateral antegrade approaches were permitted based on the patient's clinical and lesion characteristics. The reference lesion segment was defined as the most normal-looking segment located proximally or distally to the lesion, identified either angiographically or by ultrasonography. Pre-dilation was performed using a plain balloon followed by DCB angioplasty with IN.PACT Admiral (Medtronic Inc., Santa Rosa, CA, USA) DCB. When atherectomy was

conducted, additional balloon dilation for lesion preparation was not mandatory. The diameter and length of DCBs and the pre-dilation balloon were determined by the operator based on IVUS evaluation. Both intraluminal and subintimal wiring techniques were permitted for chronic total occlusion lesions. Use of atherectomy device for heavily calcified lesions and a self-expanding nitinol stent in patients with >50% residual stenosis or visible major flow-limiting dissection were at the operator's discretion.

Lesion complexity and distribution of FPA lesion were described according to the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) II. Severe calcification was defined as Peripheral artery calcium scoring system (PACCS) grade 3 or 4[15, 16]. Technical success was defined as achieving residual stenosis of <30% without flow limitation, whereas procedural success was defined as achieving technical success without any acute procedure-related complications. Dual antiplatelet therapy with aspirin and clopidogrel were recommended to be maintained for at least 90 days after index procedure. Clinical follow-up was conducted at 1, 3, 6, and 12 months following endovascular treatment. Duplex ultrasonography (DUS), computed tomography angiography (CTA), or digital subtraction angiography (DSA) were performed at 12-month follow-up.

2.3. Intravascular ultrasound data

The lumen area and external elastic membrane (EEM) area of proximal and distal reference segments, as well as the minimum lumen area (MLA), wire location (intraluminal or subintimal), and the circumference and length of calcification were assessed during pre-procedural IVUS. At the final IVUS, lumen area and EEM area at the MLA site were recorded, and the presence of any dissections, as well as their circumference and length, were determined. Plaque burden was calculated as (EEM area – lumen area) / EEM area × 100%. At totally occluded lesions, the pre-procedural lumen area was recorded as zero, and pre-dilatation was allowed prior to the first IVUS if the IVUS catheter could not pass through the lesion. All IVUS data were interpreted by interventional specialists during the index procedure and were double-checked at a core laboratory.

2.4. Study outcomes

The study endpoint was the 12-month primary patency of the target lesion, defined as an absence of clinically driven target lesion revascularization (CD-TLR) or binary restenosis on DUS, CTA, or

DSA. CD-TLR was defined as reintervention due to significant target lesion stenosis of ≥50% within 5-mm proximal or distal to the original treated segment, accompanied by recurrent symptoms or an ankle-brachial index (ABI) decrease of ≥0.15. Binary restenosis was defined as a peak systolic velocity ratio of ≥2.4 on DUS or a luminal narrowing of 50% or more on CTA or DSA. The secondary endpoints were freedom from CD-TLR and major amputation within 12 months. Safety endpoints included all-cause death, cardiovascular death, myocardial infarction, and major bleeding, assessed according to the Thrombolysis in Myocardial Infarction (TIMI) criteria[17].

2.5. Statistical analysis

Baseline clinical characteristics, lesion and procedural values, and IVUS measurement data were analyzed and compared in patients with and without patency loss. Continuous variables were presented as mean ± standard deviation and compared using a *t*-test or Mann-Whitney test. Categorial variables were presented as count (percentage) and compared using χ^2-tests or Fisher's exact test, as appropriate.

Receiver operator characteristic (ROC) curves were generated to determine the optimal cut-off value of post-procedural IVUS MLA that predicts primary patency loss at 12 months. Kaplan-Meier survival analysis was performed for primary patency at 12 months based on the "optimal cutoff" value, and the difference between groups was evaluated using the log-rank test. Individual clinical and procedural, or IVUS predictors for patency loss after DCB angioplasty were identified using a Cox proportional hazard regression model. Putative predictors with p-values <0.20 in univariate analysis were selected, and the backward stepdown elimination approach based on the Akaike information criterion (AIC) was used to construct multivariate regression model[18].

All comparisons were two-sided with $p < 0.05$ considered statistically significant. Data analysis was performed using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

3.1. Study patients

Among the 98 subjects included in our analysis, 82 patients maintained primary patency at 12 months, and 16 patients experienced patency loss within 12-month follow-up period. Patients in the patency-loss group were younger (mean age 65.0 vs. 70.4). However, other characteristics—including previous conditions, such as diabetes, chronic kidney disease, and coronary artery disease, as well as clinical presentation (e.g., claudication or chronic limb-threatening ischemia), pre-procedural ABI values, and medications at discharge—were similar between the two groups (Table 1).

Table 1. Baseline patient characteristics

Characteristics	Patency-maintained (n=82)	Patency-loss (n=16)	p-value
Age, years	70.4 ± 8.1	65.0 ± 10.1	0.023
Male	67 (81.7)	15 (93.8)	0.411
Body mass index, kg/m^2	23.7 ± 3.4	24.9 ± 3.5	0.339
Current smoker	25 (30.5)	4 (25.0)	0.888
Hypertension	64 (78.0)	13 (81.2)	1.000
Diabetes	49 (59.8)	9 (56.2)	1.000
Dyslipidemia	61 (74.4)	11 (68.8)	0.875
Chronic kidney disease	19 (23.2)	4 (25.0)	1.000
End stage renal disease on hemodialysis	8 (9.8)	4 (25.0)	0.199
Coronary artery disease	31 (37.8)	4 (25.0)	0.489
Prior stroke	8 (9.8)	2 (12.5)	1.000
Clinical presentation			0.124
Claudication	59 (72.0)	15 (93.8)	
CLTI	23 (28.0)	1 (6.2)	
Pre-procedural ABI	0.56 ± 0.18	0.56 ± 0.16	0.998

Medication at discharge			
Aspirin	80 (97.6)	15 (93.8)	0.987
Clopidogrel	81 (98.8)	15 (93.8)	0.737
Cilostazol	34 (41.5)	6 (37.5)	0.986
Statin	79 (96.3)	13 (81.2)	0.083

Continuous values are presented as mean ± standard deviation, and categorial variables are presented as number (%).
Abbreviations: ABI, ankle-brachial index; CLTI, chronic limb-threatening ischemia; EVT, endovascular treatment

3.2. Clinical outcomes

At the 12-month follow-up, 16 patients experienced loss of primary patency. Among them, nine cases were classified as having CD-TLR, and the remaining 7 cases exhibited binary restenosis, as confirmed by DUS. No major amputation was recorded, and only two patients underwent minor amputations. Seven patients died during the follow-up period. Causes of death included cardiac death (three patients), underlying malignancy (two patients), and intracranial hemorrhage (one patient), as well as one death due to an unknown cause. Two bleeding events were recorded, one intracranial hemorrhage and one gastrointestinal bleed (Appendix 2).

3.3. Procedural result and study outcomes

Lesion characteristics are summarized in Table 2. Approximately 70% of enrolled subjects had TASC-II type C or D (67.1% vs. 75.0% in the patency-maintained and patency-loss groups, respectively, p=0.742) lesions. The mean lesion length of 220.2 mm in the patency-maintained group and 226.6 mm in the patency-loss group. Over 65% of the target lesions were totally occluded, and severe calcification was observed in 50.0% and 37.5% of patients in the patency-maintained and patency-loss groups, respectively (p = 0.521). This trend remained consistent upon the application of CD-TLR (Appendix 3).

The use of atherectomy devices, as well as the sizes of plain balloons and DCBs, were similar between the two groups. However, in the patency-loss group, fewer patients underwent angioplasty with intraluminal wiring (74.4% vs. 43.8%, p = 0.033, patency-maintained group and patency-loss group, respectively). Patients with patency-loss also had a higher rate of bail-out stenting (17.1% vs.

50.0%, p = 0.010), more frequent use of adjuvant ballooning (17.1% vs. 43.8%, p = 0.010), and a lower post-procedural ABI (1.00 vs. 0.89, p = 0.001) than those in the patency-maintained group.

IVUS measurements obtained prior to DCB treatment, including proximal, distal, and mean reference vessel size, lumen area, and degree of calcification data, were similar in both groups. However, analysis of post-procedural IVUS data revealed that patency-maintained group demonstrated a larger MLA (13.64 mm^2 vs. 11.34 mm^2, p = 0.009), lower plaque burden at the MLA site (57% vs. 68%, p <0.001), and a higher MLA per mean reference EEM area (0.41 vs. 0.30, p = 0.001) (Table 3).

Table 2. Lesion and procedural characteristics

Characteristics	Patency-maintained (n=82)	Patency-loss (n=16)	p-value
TASC-II type C/D	55 (67.1)	12 (75.0)	0.742
Lesion length, mm	220.2 ± 118.3	226.6 ± 152.0	0.852
Total occlusion	53 (65.4)	11 (73.3)	0.766
Severe calcification [a]	41 (50.0)	6 (37.5)	0.521
Popliteal artery involvement	7 (8.5)	3 (18.8)	0.434
Poor BTK run-off [b]	21 (25.6)	5 (31.2)	0.875
Intraluminal wiring	61 (74.4)	7 (43.8)	**0.033**
Atherectomy	28 (34.1)	3 (20.0)	0.436
Pre-balloon diameter, mm	5.0 ± 0.9	5.3 ± 0.5	0.196
Pre-balloon pressure, mmHg	11.8 ± 4.1	11.4 ± 2.5	0.673
Mean DCB diameter, mm	5.6 ± 0.6	5.6 ± 0.7	0.943
Maximum DCB diameter, mm	5.8 ± 0.7	5.7 ± 0.8	0.768
Bailout stenting	14 (17.1)	8 (50.0)	**0.010**
Adjuvant ballooning	14 (17.1)	7 (43.8)	**0.041**
Dissection	50 (61.0)	8 (50.0)	0.590
Residual stenosis > 30%	19 (23.2)	5 (32.2)	0.072
Technical success			0.072

Suboptimal	19 (23.2)	5 (32.2)	
Successful	63 (77.8)	11 (8.8)	
Post-procedural ABI	1.01 ± 0.12	0.89 ± 0.10	**0.001**

Continuous values are presented as mean ± standard deviation, and categorial variables are presented as number (%).
[a] Peripheral artery calcium scoring system (PACCS) 3 and 4.
[b] Number of patent arteries below the knee artery = 0 or 1.
Abbreviations: ABI, ankle-brachial index; BTK, below the knee; DCB, drug-coated balloon; SFA, superficial femoral artery; TASC, Trans-Atlantic Inter-Society Consensus

Table 3. Pre- and post-procedural IVUS data

Values	Patency-maintained (n=82)	Patency-loss (n=16)	p-value
Proximal reference EEM area, mm^2	40.52 ± 12.52	44.83 ± 12.99	0.213
Proximal reference lumen area, mm^2	23.29 ± 7.83	25.98 ± 11.79	0.253
Distal reference EEM area, mm^2	29.09 ± 7.21	32.54 ± 9.40	0.100
Distal reference lumen area, mm^2	16.73 ± 4.86	18.08 ± 7.64	0.362
Mean reference EEM area, mm^2	34.80 ± 8.49	38.69 ± 10.78	0.113
Mean reference lumen area, mm^2	20.01 ± 5.37	22.03 ± 8.29	0.214
Intraluminal wiring	59 (72.0)	9 (57.2)	0.342
Calcium angle > 270, number (%)	21 (25.6)	5 (31.2)	0.875
EEM area ate MLA site, mm^2	32.93 ± 7.56	35.00 ± 8.66	0.330
MLA, mm^2	13.64 ± 2.86	11.34 ± 4.44	**0.009**
Plaque burden [a] at MLA site (%)	57 ± 10	68 ± 9	**<0.001**
MLA / Mean reference EEM area [b]	0.41 ± 0.11	0.30 ± 0.12	**0.001**
Edge dissection	34 (41.5)	8 (50.0)	0.723
Dissection length > 50% of lesion length	3 (3.7)	2 (12.5)	0.396
Dissection circumference> 180°	8 (9.8)	6 (37.5)	**0.012**

Continuous values are presented as mean ± standard deviation, and categorial variables are presented as number (%).
[a] Plaque burden: (EEM area – lumen area) / EEM area × 100%
[b] Mean reference area: (Proximal reference vessel EEM or lumen area + distal reference vessel EEM or lumen area)/2.

EEM: external elastic membrane; MLA: minimum lumen area.

3.4. Intravascular ultrasound parameter analysis

Following DCB treatment for FPA disease, individual IVUS parameter were analyzed to identify potential predictors for patency loss. Among these parameters, the minimum stent area (MSA), previously reported as a significant IVUS-derived predictor and commonly used by operators as a key procedural endpoint, was further assessed using ROC curve analysis.

ROC curve analysis identified an optimal post-procedural MLA cut-off of 11.6 mm^2 for predicting primary patency at 12 months (area under the ROC curve [AUC]: 0.685, 95% CI: 0.513-0.857). This cut-off resulted in a sensitivity of 56% and a specificity of 81% (Figure 2).

Primary patency loss occurred in 10.6% of patients with an MLA $\geq$11.6 mm^2 (event number = 8, 12-month estimated risk = 19.2%), compared to 34.8% of patients with an MLA <11.6 mm^2 (event number = 8, 12-month estimated risk = 39.0%), yielding a 19.8% greater absolute risk of patency loss in those below the 11.6 mm^2 cut-off (95% CI: 3.4 to 44.7, p <0.001; Figure 3).

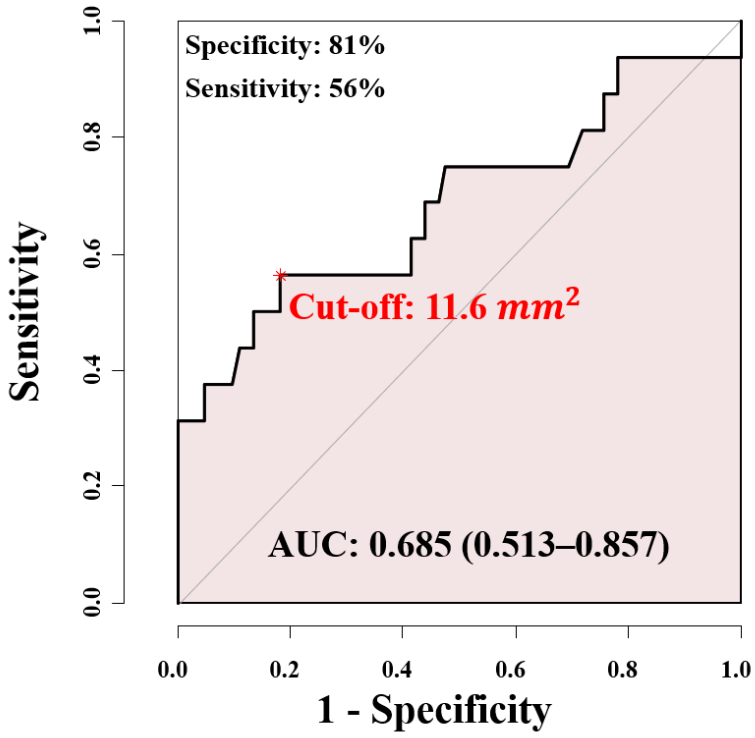


Figure 2. Receiver operating characteristics curve of post-procedural intravascular ultrasound minimum lumen area.
The optimal cut-off value was identified as 11.6 mm^2, with a sensitivity of 56% and specificity of 81%.
Abbreviations: AUC, Area under curve.

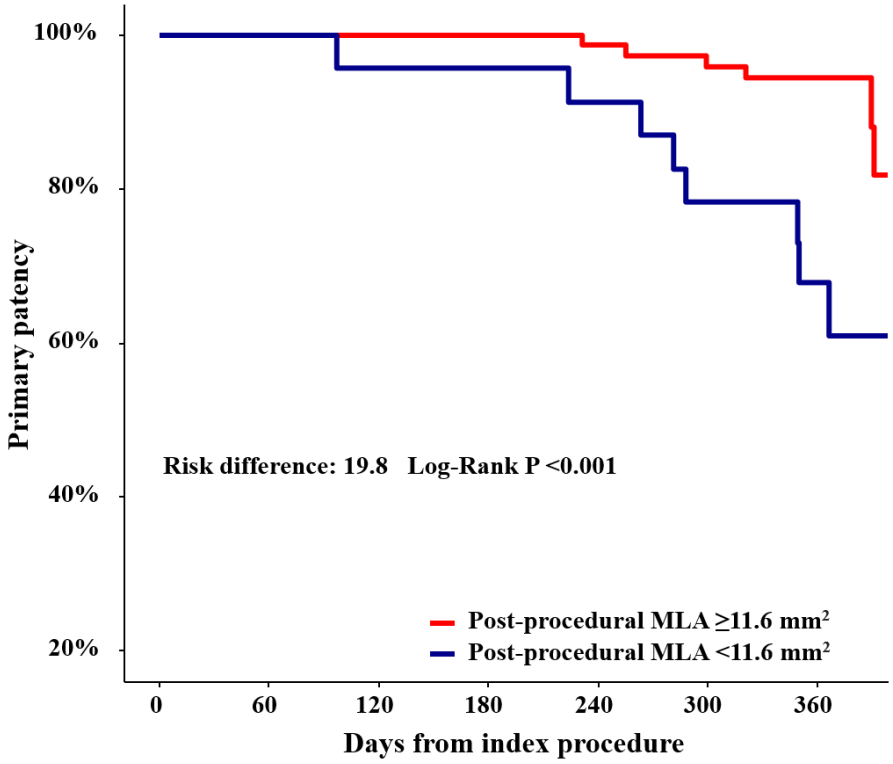


Figure 3. Kaplan-Meier curve for primary patency based on post-procedural minimum lumen area (MLA)

3.5. Predictors of patency loss

As presented in Table 4, results of univariate and multivariate Cox regression analysis showed that end-stage renal disease on hemodialysis (adjusted hazard ratio: 6.18, 95% CI: 1.56-24.49, p = 0.009), bail-out stenting for residual stenosis or flow-limiting dissection (adjusted hazard ratio: 5.11, 95% CI: 1.56-16.65, p-value = 0.007), and post-procedural dissection length >50% (adjusted hazard ratio: 6.83, 95% CI: 1.15-40.37, p-value = 0.034) were individual predictors for an increased risk of patency loss. Among the potential IVUS indicators, post-procedural MLA ≥11.6 mm^2 was associated with a significantly lower risk of patency loss (adjusted hazard ratio: 0.27, 95% CI: 0.09-0.80, p-value = 0.019).

Table 4. Predictors of loss of primary patency at 12months

	Univariate		Multivariate	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Clinical data				
Age (per 1 year)	0.94 (0.89-1.00)	**0.059**	0.95 (0.89-1.01)	0.095
Female	0.35 (0.05-2.67)	0.312		
Body mass index, kg/m^2	1.04 (0.89-1.21)	0.624		
Hypertension	1.03 (0.29-3.70)	0.963		
Current smoker	0.58 (0.19-1.83)	0.355		
Diabetes	0.89 (0.33-2.39)	0.816		
Chronic kidney disease	0.94 (0.30-2.95)	0.911		
ESRD on hemodialysis	4.18 (1.26-13.89)	**0.020**	6.18 (1.56-24.49)	**0.009**
CLTI	0.18 (0.02-1.38)	**0.098**	0.20 (0.02-2.43)	0.209
Dyslipidemia	0.93 (0.32-2.22)	0.891		
Lesion and procedural data				
TASC-II type D	1.29 (0.45-3.70)	0.630		
Popliteal artery involvement	1.72 (0.48-6.17)	0.403		
Lesion length> 150mm	1.68 (0.53-5.33)	0.377		
Mean RVD, mm	1.26 (0.57-2.76)	0.561		
Severe calcification [a]	0.41 (0.11-1.45)	**0.164**		
Total occlusion	1.02 (0.31-3.35)	0.970		
Mean DCB diameter (per 0.1mm)	0.98 (0.90-1.08)	0.763		
Poor BTK run-off [b]	0.87 (0.27-2.80)	0.818		
Subintimal wiring	3.71 (1.32-10.45)	**0.013**		
Atherectomy	0.43 (0.12-1.53)	**0.191**		
Presence of dissection	0.69 (0.26-1.84)	0.455		
Residual stenosis> 30%	1.41 (0.44-4.60)	0.565		
Bailout stenting	4.81 (1.73-13.39)	**0.003**	5.11 (1.56-16.65)	**0.007**
IVUS parameters				
Proximal reference lumen area, mm^2 (per 1.0 mm^2)	1.02 (0.97-1.07)	0.389		
Proximal reference EEM area, mm^2 (per 1.0 mm^2)	1.02 (0.98-1.06)	0.378		
Distal reference lumen area, mm^2 (per 1.0 mm^2)	1.06 (0.96-1.16)	0.225		
Distal reference EEM area, mm^2 (per 1.0 mm^2)	1.04 (0.98-1.10)	0.236		
Calcium angle> 270 °	1.06 (0.36-3.13)	0.913		
Post-procedural MLA site EEM area, mm^2 (per 1.0mm^2)	1.00 (0.99-1.01)	0.319		
Post-procedural MLA≥ 11.6mm^2	0.19 (0.07-0.56)	**0.002**	0.27 (0.09-0.80)	**0.019**
Post-procedural edge dissection	1.72 (0.62-4.79)	0.297		

Post-procedural length > 50%	dissection	4.55 (0.99-20.83)	**0.051**	6.83 (1.15-40.37)	**0.034**
Post-procedural dissection circumference> 50%	maximum	4.78 (1.68-13.61)	**0.003**		

[a] Peripheral artery calcium scoring system (PACCS) 3 and 4.
[b] Number of patent arteries below the knee artery = 0 or 1.
Abbreviations: BTK, below the knee; CLTI, chronic limb-threatening ischemia; DCB, drug-coated balloon; EEM, external elastic membrane; ESRD, end-stage renal disease; HR, hazard ratio; MLA, minimum lumen area; RVD, reference vessel diameter; TASC, Trans-Atlantic Inter-Society Consensus

4. DISCUSSION

Results from this study identify post-procedural MLA, assessed by IVUS, as an independent predictor of sustained patency following DCB angioplasty in the FPA. Specifically, we found that patients with a post-procedural target lesion MLA of ≥11.6 mm^2 exhibited significantly higher 12-month primary patency than those with MLA <11.6 mm^2. Our data further indicate that end-stage renal disease, the need for bail-out stenting, and post-procedural dissection length >50% are associated with an increased risk of patency loss.

Recent randomized controlled trials have shown that IVUS guidance significantly improves primary patency after DCB angioplasty in FPA lesions relative to guidance by angiography[14, 19]. In the IVUS-DCB trial, more aggressive pre- and post-procedural vessel dilation with larger balloons and higher pressures were employed in the patients who underwent IVUS guidance, resulting in a larger post-procedural lumen diameter and improved hemodynamics, as indicated by the ABI, without increasing complications. Moreover, results from the IVUS-DCB trial identified post-procedural MLA as an independent predictor of restenosis.

The value of intravascular imaging in coronary artery interventions is widely recognized, and the use of this approach is strongly recommended in complex cases[20, 21]. Consistent with findings from the IVUS-DCB trial, previous studies have shown that achieving a larger post-procedural lumen area, measured as minimum stent area (MSA) or relative MSA to the distal reference diameter, reduces the risk of restenosis after percutaneous coronary intervention[10, 22]. Thus, IVUS guidance led to larger lumen dimensions at the target lesion by enabling optimization with larger

balloons, stents, higher inflation pressures, and additional balloon dilation[23].

In the present study, a post-procedural MLA of 11.6 mm^2 was identified as the threshold for improved primary patency at the 12-month follow-up after DCB angioplasty. In a separate retrospective investigation of patients who underwent DCB angioplasty, Horie et al. suggested an MLA cut-off of 12.7 mm^2 as a predictor to prevent restenosis[24]. We note that both studies included a small number of patients with differing clinical and lesion characteristics. However, most target lesions (73.9%) assessed by Horie et al. were classified as TASC-II A or B, and exhibited a shorter lesion length than those in our study (approximately 90 mm vs. 220mm). Furthermore, no provisional stenting was performed. These factors likely contributed to the higher optimal post-procedural MLA cut-off identified in their analysis.

Beyond achieving a sufficient post-procedure lumen area, other IVUS parameters, including a calcification circumference of $\geq 270^{o}$ and a small distal EEM diameter (<5 mm), were previously identified as significant predictors of increased risk for restenosis after DCB angioplasty in the FPA[25]. Additionally, lesion characteristics, such as longer length, involvement of the popliteal artery, and total occlusion, have been reported as predictors of restenosis after DCB angioplasty[26]. Kurata et al. found that selecting DCB size based on the IVUS-evaluated EEM diameter rather than the lumen diameter determined by angiography or IVUS was associated with a lower risk of restenosis in FPA lesions[27]. Therefore, optimizing lesions before and after DCB angioplasty based on IVUS-measured EEM dimensions is recommended[28]. Our findings further suggest that achieving an MLA of at least 11.6 mm^2 is critical for improving outcomes following DCB angioplasty.

A recent large Japanese study reported an increased incidence of aneurysmal degeneration following IVUS-guided fluoropolymer-based drug-eluting stent angioplasty, likely due to the use of larger devices[29, 30]. This phenomenon is thought to result from vascular injury and inflammation caused by aggressive dilation, combined with prolonged drug elution and the continuous expansion of the metallic scaffold. In contrast, this effect was not observed in our study population, possibly due to the DCBs shorter drug-release time and the absence of a continuously expanding metal scaffold. Thus, our results are consistent with prior studies showing that IVUS-guided DCB angioplasty is safe.

5. Limitations

Several limitations of this study should be noted. First, the study included a relatively small number of patients, which may limit the statistical power of the analysis. Second, only FPA lesions treated with DCB angioplasty were assessed, and thus, our conclusions may primarily apply to FPA lesions treated via this modality. Third, the study population consisted solely of Korean patients; therefore, the post-procedural MLA threshold identified here for improved primary patency may not be directly applicable to patients of other ethnicities, as vessel size can vary with body size. Finally, patient follow-up was limited to 12 months.

6. CONCLUSION

Results from this study indicate that achieving a sufficient post-procedural lumen area is crucial for maintaining primary patency in target FPA lesions after DCB angioplasty. Specifically, a post-procedural MLA of $\geq$11.6 mm^2 was identified as the optimal cut-off value for predicting lesion patency, below which the risk of patency loss is significantly increased.

References

1. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;69:e71-e126.
2. Feldman DN, Armstrong EJ, Aronow HD, Gigliotti OS, Jaff MR, Klein AJ et al. SCAI consensus guidelines for device selection in femoral-popliteal arterial interventions. Catheter Cardiovasc Interv. 2018;92:124-140.
3. Chowdhury MM, Singh K, Albaghdadi MS, Khraishah H, Mauskapf A, Kessinger CW et al. Paclitaxel Drug-Coated Balloon Angioplasty Suppresses Progression and Inflammation of Experimental Atherosclerosis in Rabbits. JACC Basic Transl Sci. 2020;5:685-695.
4. Giacoppo D, Cassese S, Harada Y, Colleran R, Michel J, Fusaro M, et al. Drug-Coated Balloon Versus Plain Balloon Angioplasty for the Treatment of Femoropopliteal Artery Disease: An Updated Systematic Review and Meta-Analysis of Randomized Clinical Trials. JACC Cardiovasc Interv. 2016;9:1731-1742.
5. Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med. 2015;373:145-153.
6. Bausback Y, Wittig T, Schmidt A, Zeller T, Bosiers M, Peeters P, et al. Drug-Eluting Stent Versus Drug-Coated Balloon Revascularization in Patients With Femoropopliteal Arterial Disease. J Am Coll Cardiol. 2019;73:667-679.
7. Liistro F, Angioli P, Porto I, Ducci K, Falsini G, Ventoruzzo G, et al. Drug-Eluting Balloon Versus Drug-Eluting Stent for Complex Femoropopliteal Arterial Lesions: The DRASTICO Study. J Am Coll Cardiol. 2019;74:205-215.
8. Lee SJ, Lee HH, Ko YG, Ahn CM, Lee YJ, Kim JS, et al. Device Effectiveness for Femoropopliteal Artery Disease Treatment: An Analysis of K-VIS ELLA Registry. JACC Cardiovasc Interv. 2023;16:1640-1650.
9. Secemsky EA, Mosarla RC, Rosenfield K, Kohi M, Lichtenberg M, Meissner M, et al. Appropriate Use of Intravascular Ultrasound During Arterial and Venous Lower Extremity Interventions. JACC Cardiovasc Interv. 2022;15:1558-1568.

10. Schuurman AS, Vroegindewey MM, Kardys I, Oemrawsingh RM, Garcia-Garcia HM, van Geuns RJ, et al. Prognostic Value of Intravascular Ultrasound in Patients With Coronary Artery Disease. J Am Coll Cardiol. 2018;72:2003-2011.
11. Gao XF, Ge Z, Kong XQ, Chen X, Han L, Qian XS, et al. Intravascular Ultrasound vs Angiography-Guided Drug-Coated Balloon Angioplasty: The ULTIMATE Ⅲ Trial. JACC Cardiovasc Interv. 2024;17:1519-1528.
12. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, et al. Effect of Intravascular Ultrasound-Guided vs Angiography-Guided Everolimus-Eluting Stent Implantation: The IVUS-XPL Randomized Clinical Trial. JAMA. 2015;314:2155-2163.
13. Divakaran S, Parikh SA, Hawkins BM, Chen S, Song Y, Banerjee S, et al. Temporal Trends, Practice Variation, and Associated Outcomes With IVUS Use During Peripheral Arterial Intervention. JACC Cardiovasc Interv. 2022;15:2080-2090.
14. Ko YG, Lee SJ, Ahn CM, Lee SH, Lee YJ, Kim BK, et al. Intravascular ultrasound-guided drug-coated balloon angioplasty for femoropopliteal artery disease: a clinical trial. Eur Heart J. 2024;45:2839-2847.
15. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33 Suppl 1:S1-75.
16. Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. Catheter Cardiovasc Interv. 2014;83:E212-220.
17. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011 ;123:2736-47.
18. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1-73.
19. Allan RB, Puckridge PJ, Spark JI, Delaney CL. The Impact of Intravascular Ultrasound on Femoropopliteal Artery Endovascular Interventions: A Randomized Controlled Trial. JACC Cardiovasc Interv. 2022 ;15:536-546.
20. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC

Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45:3415-3537.

21. Lee JM, Choi KH, Song YB, Lee JY, Lee SJ, Lee SY, et al. Intravascular Imaging-Guided or Angiography-Guided Complex PCI. N Engl J Med. 2023;388:1668-1679.
22. Fujimura T, Matsumura M, Witzenbichler B, Metzger DC, Rinaldi MJ, Duffy PL, et al. Stent Expansion Indexes to Predict Clinical Outcomes: An IVUS Substudy From ADAPT-DES. JACC Cardiovasc Interv. 2021;14:1639-1650.
23. Konishi H, Habara M, Nasu K, Koshida R, Kinoshita Y, Tsuchikane E, et al. Impact of Optimal Preparation Before Drug-Coated Balloon Dilatation for De Novo Lesion in Patients With Coronary Artery Disease. Cardiovasc Revasc Med. 2022;35:91-95.
24. Horie K, Tanaka A, Taguri M, Inoue N. Impact of Baseline and Postprocedural Intravascular Ultrasound Findings on 1-Year Primary Patency After Drug-Coated Balloon Treatment of Femoropopliteal Lesions. J Endovasc Ther. 2022;29:66-75.
25. Toyoshima T, Iida O, Takahara M, Okamoto S, Ishihara T, Nanto K, et al. Factors Associated With Early and Late Restenosis Following Drug-Coated Balloon Treatment for Patients With Femoropopliteal Lesions. J Endovasc Ther. 2023:15266028231186717.
26. Soga Y, Takahara M, Iida O, Tomoi Y, Kawasaki D, Tanaka A, et al. Vessel Patency and Associated Factors of Drug-Coated Balloon for Femoropopliteal Lesion. J Am Heart Assoc. 2023;12:e025677.
27. Kurata N, Iida O, Takahara M, Asai M, Masuda M, Okamoto S, et al. Clinical Impact of the Size of Drug-Coated Balloon Therapy on Restenosis Rate in Femoropopliteal Lesions. Journal of Endovascular Therapy. 2022;30:269-280.
28. Kurata N, Iida O, Asai M, Okamoto S, Ishihara T, Nanto K, et al. Factors in Sufficient Endovascular Vessel Preparation for Severely Calcified Femoropopliteal Lesions. Circ J. 2023;87:424-431.
29. Iida O, Takahara M, Soga Y, Yamaoka T, Fujihara M, Kawasaki D, et al. 1-Year Outcomes of Fluoropolymer-Based Drug-Eluting Stent in Femoropopliteal Practice: Predictors of Restenosis and Aneurysmal Degeneration. JACC Cardiovasc Interv. 2022;15:630-638.
30. Tsujimura T, Iida O, Takahara M, Soga Y, Yamaoka T, Fujihara M, et al. Clinical Impact of Intravascular Ultrasound-Guided Fluoropolymer-Based Drug-Eluting Stent Implantation for

Femoropopliteal Lesions. JACC Cardiovasc Interv. 2022;15:1569-1578.

Appendix 1. Inclusion and exclusion criteria

Inclusion criteria
Age 19 or older
Symptomatic peripheral artery disease

- Moderate or severe claudication (Rutherford classification grade 2 or 3) or
- Critical limb threatening ischemia (Rutherford classification grade 4 or 5)

Stenosis of more than 50% of the femoropopliteal artery
Ankle-brachial index <0.9
Patients who signed the informed consent form

Exclusion criteria
Acute severe lower extremity ischemia
Severe critical limb ischemia (Rutherford classification grade 6)
Known hypersensitivity or contraindications to the following medicines: heparin, aspirin, clopidogrel, cilostazol, or contrast media
Patients who need to take oral anticoagulants such as warfarin or NOAC
Age >85 years old
Severe liver function abnormality (more than 3 times the normal reference value)
Significant leukopenia, neutropenia, thrombocytopenia, anemia or known hemorrhagic tendency
Left ventricular ejection fraction <40% or clinically evident congestive heart failure
Pregnant women or women of childbearing age
Patients with an expected life expectancy of less than 1 year due to comorbidities.
Patients with a history of bypass surgery or stent insertion involving the target femoropopliteal artery
When there is a lesion with >50% stenosis above the target femoropopliteal artery lesion (iliac artery or proximal femoral artery) without revascularization

- The subject can be enrolled if the inflow lesion is performed concomitantly with the target femoropopliteal artery lesion

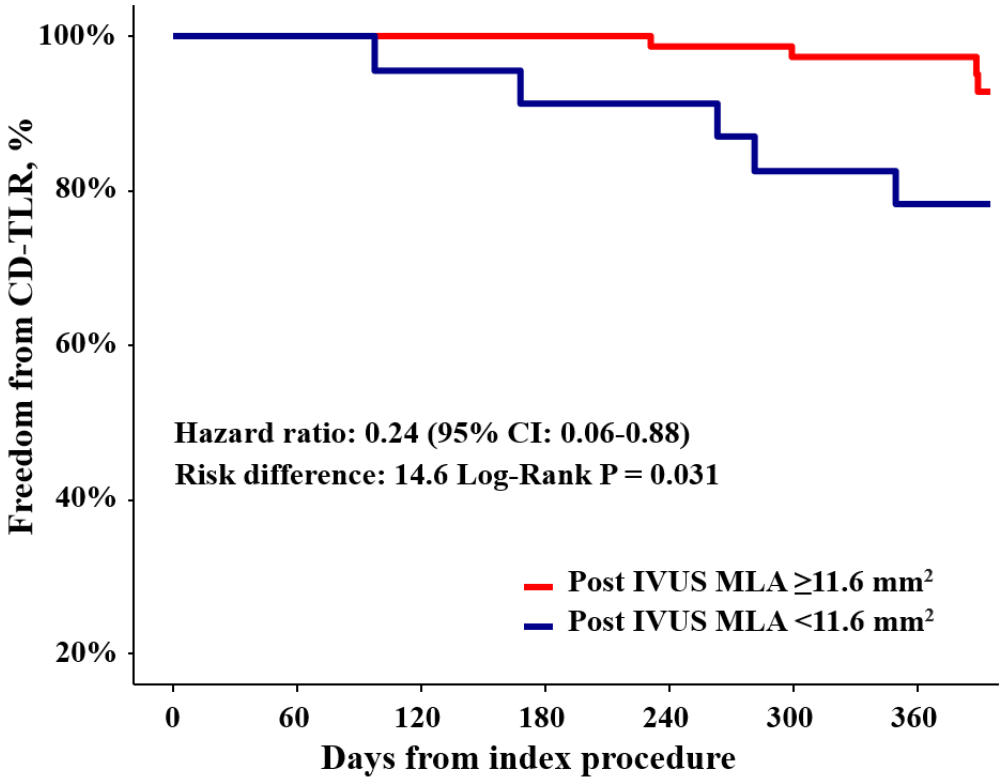
Abbreviation: NOAC, Non-vitamin K antagonist oral anticoagulant

Appendix 2. Clinical outcomes at 12-month follow-up

Outcomes	Event no./total no. (%)
Primary endpoint	
Primary patency	82/98 (83.7)
Secondary endpoints	
Freedom from CD-TLR	89/98 (90.8)
Freedom from major amputation	98/98 (100.0)
Safety endpoints	
All-cause death	7/118 (5.9)
Cardiovascular death	3/118 (2.5)
Myocardial infarction	0 (0)
Major bleeding	2/118 (1.7)

*Safety endpoints were analyzed in the entire enrolled patient population.
Abbreviations: CD-TLR, Clinically-driven target lesion revascularization

Appendix 3.



Kaplan-Meier curve for freedom from CD-TLR rate, based on post-procedural minimum lumen area

Abbreviations: MLA, Minimum lumen area; CD-TLR, Clinically-driven target lesion revascularization

Abstract in Korean

대퇴슬와동맥 병변에 대한 약물 코팅 풍선 치료 후 임상적, 혈관 조영술적 재협착 발생에 대한 혈관 내 초음파 예측인자 모델 수립: IVUS-DCB 다기관 무작위 연구 사후분석

배경: 혈관 내 초음파(IVUS)는 대퇴슬와동맥(FPA)병변에 대한 약물 코팅 풍선(DCB)을 이용한 혈관성형술의 치료 성적을 향상시키는 것으로 알려져 있다. 하지만 대퇴슬와동맥 병변에서 약물 코팅 풍선을 이용한 혈관성형술의 예후를 개선하기 위한 최적의 혈관 내 초음파 기준은 아직 명확히 적립되지 않았다.

방법: 본 연구는 대퇴슬와동맥 병변에 대한 약물 코팅 풍선을 이용한 혈관성형술 후 12개월 이내에 혈관 개통성(patency) 상실을 예측할 수 있는 혈관 내 초음파 인자를 규명하는 것을 목적으로 하였다. 혈관 내 초음파 데이터가 불충분했던 1명을 제외하고, IVUS-DCB 무작위 임상시험의 혈관 내 초음파 유도 시술군에 포함된 98명이 분석에 포함되었다. 12개월째 혈관 개통성 상실을 예측하는 혈관 내 초음파 지표와 이들의 최적 절단값 (cut-off value)을 분석하였다.

결과: 혈관 내 초음파 유도하에 대퇴슬와동맥 중재시술을 받은 98명 중 16명(16.3%)은 12개월 이내에 일차적 개통성을 상실하였다. 혈액투석 중인 말기 신부전, 구제목적의 스텐트 삽입 (bail-out stent), 시술 후 박리(dissection) 길이가 50%를 초과한 경우는 12개월째 개통성 상실의 독립적인 시술 예측 인자였다. ROC 곡선 분석에서, 시술 후 최소 내강 면적이 ≥11.6 mm^2 이 일차적 개통성 유지의 최적 절단값으로 나타났으며, ROC 곡선 아래 면적은 0.685 (95% CI: 0.513-0.857)였다. 생존 분석에서는 최소 내강 면적 ≥11.6 mm^2 인 경우 개통성 상실 위험이 낮았으며, 해당 집단의 위험비는 0.27 (95% CI: 0.09-0.80, p=0.019, 위험 차이: 19.8)로 확인되었다. 시술 후 최소 내강 면적 ≥11.6 mm^2 는 대퇴슬와동맥 병변 환자에서 약물 방출 풍선 혈관성형술 후 일차 개통성 유지의 독립적인 혈관 내 초음파 예측 인자로 확인되었다.

결론: 본 연구 결과는 약물 코팅 풍선 혈관성형술 시 혈관 내 초음파 유도 하에 병변을 최적화하고 충분한 내강 면적을 확보하는 것이 목표 혈관의 개통성을 유지하는 데 중요함을 시사한다.

핵심 단어: 대퇴슬와동맥 병변, 약물 코팅 풍선, 혈관 내 초음파