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Clinical Outcomes of Subintimal vs. Intraluminal Revascularization Approaches for Long Femoropopliteal Occlusions in a Korean Multicenter Retrospective Registry Cohort

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Background: There are limited data comparing the outcomes of subintimal vs. intraluminal approach in the treatment of long femoropopliteal artery occlusions. The objective of this study was to investigate the efficacy and safety of the subintimal approach for long femoropopliteal artery occlusions.

Methods and Results: From a multicenter retrospective registry cohort, we included a total of 461 patients with 487 femoropopliteal artery occlusions classified as Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) II C/D for this analysis. We compared the immediate and mid-term outcomes of subintimal vs. intraluminal approaches. There were 228 patients with 243 limbs in the subintimal group, and 233 patients with 244 limbs in the intraluminal group. Baseline clinical and lesion characteristics were comparable between the 2 groups. The technical success rate was significantly higher in the subintimal group than in the intraluminal group (95.1% vs. 89.8%, P=0.041). The clinical primary patency (67.5% vs. 73.4% at 12 months, 54.0% vs. 61.3% at 24 months; P=0.086) and target lesion revascularization (TLR)-free survival (89.5% vs. 86.3% at 12 months, 77.6% vs. 76.0% at 24 months; P=0.710) did not differ significantly between the subintimal and the intraluminal groups.

Conclusions: In long femoropopliteal occlusions, the subintimal approach achieved a higher technical success rate and similar mid-term primary patency and TLR-free survival compared with intraluminal approach.

Key Words: Chronic total occlusion; Femoropopliteal artery; Peripheral artery disease; Revascularization; Subintimal angioplasty

The femoropopliteal artery is the longest arterial segment that is exposed to various forces induced by leg movements and frequently affected by the atherosclerotic process. Over the past decade, self-expanding nitinol stents have significantly improved the outcomes of endovascular therapy for femoropopliteal artery disease;[1] however, the technical success and durability of patency after endovascular treatment in this arterial segment have been challenged by common lesion characteristics, such as long occlusions and calcifications.[2]

The subintimal approach is a technique that recanalizes a totally occluded segment via intentional creation of a subintimal channel. Since this approach was first described by Bolia et al in 1989,[3] the subintimal approach has been widely used to overcome long chronic arterial occlusions.[2,4–6] Furthermore, the more recent introduction of re-entry devices and the adoption of bidirectional wiring approaches have improved the technical success of the subintimal approach for femoropopliteal lesions.[7] In addition, implantation of self-expanding nitinol stents further contributes to increased patency rates after this procedure.[1,7–9] Despite these recent advances in the outcomes of the subintimal

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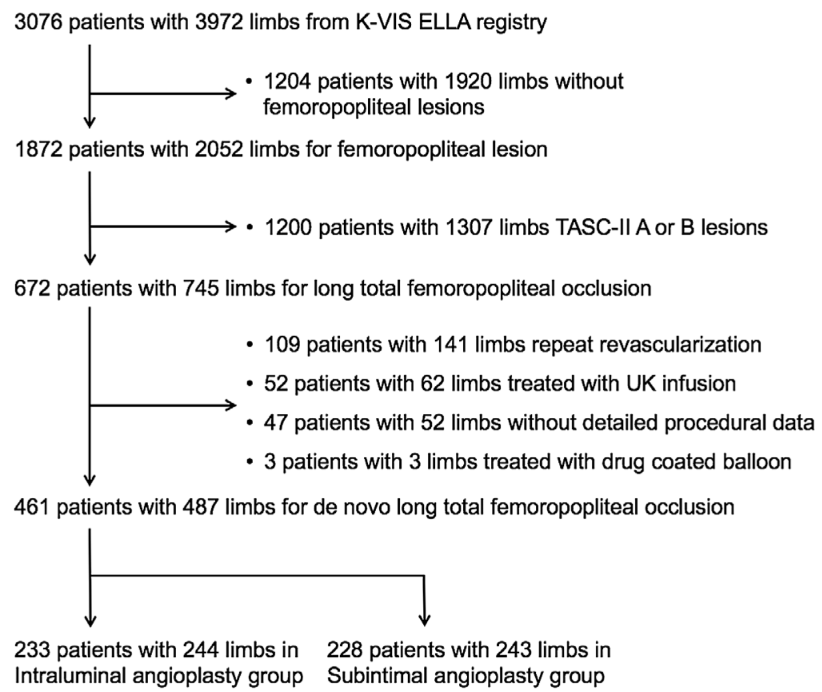

Figure 1. Study flowchart. TASC, Inter-Society Consensus for the Management of Peripheral Arterial Disease; UK, urokinase.

approach, there is still concern about the durability of the subintimally created channel. Most of the previous studies on the subintimal approach have been single-center retrospective studies with relatively small numbers of patients.[10]

Furthermore, there are only limited data comparing the outcomes of the subintimal vs. intraluminal approach in the treatment of long femoropopliteal artery occlusions. Thus, in the present study, we sought to investigate the immediate and mid-term outcomes of the subintimal approach for the treatment of femoropopliteal chronic occlusion by analyzing data from a multicenter registry cohort.

Methods

Study Population

The Korean Vascular Intervention Society (K-VIS) Endovascular therapy in Lower Limb Artery diseases registry (ELLA) is a multicenter observational study with retrospective and prospective cohorts of patients with lower extremity artery disease treated with endovascular therapy (ClinicalTrials.gov NCT02748226). The retrospective patient cohort consisted of 3,434 patients with 5,097 affected limbs treated between January 2006 and July 2015 in 31 Korean hospitals.[11] Inclusion criteria were: age ≥20 years, and lower extremity artery disease treated with endovascular therapy. Acute limb ischemia, Buerger's disease, repeated revascularization after the first index procedure, and patients without procedural, in-hospital, or first clinical follow-up data were excluded. We further excluded patients (n=3) treated with drug-coated balloons, which have shown superior outcomes than plain conventional balloons in terms of primary patency and target lesion revascularization (TLR)-free survival.[12] There were no cases of treatment with drug-eluting stents or interwoven nitinol stents. From this registry population, the present study analyzed a total of 461 patients (487 limbs) with the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) II C or D de novo femoropopliteal artery occlusions (**Figure 1**). Data for patients' baseline clinical and lesion characteristics, medications at hospital discharge, clinical status at follow-up, and non-invasive and invasive investigations were collected from their electronic medical records. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of the participating hospitals. The associated institutional review boards waived the requirement for informed consent for this retrospective study.

Angioplasty Procedures and Follow-up

Dual-antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) was administered prior to the index procedure. All procedures were performed under local anesthesia and supplemented with intravenous sedation and analgesia when required. Systemic heparin (5,000 units) was administered to achieve an activated clotting time >250 s. Either ipsilateral or contralateral femoral puncture was performed, depending on the distance to the target lesion.

The choice of intraluminal or subintimal approach was left to the operator's discretion. For the intraluminal approach, various 0.014-, 0.018-, and 0.035-inch guidewires were chosen according to lesion characteristics and operator's preference. For the subintimal approach, 0.018- or 0.035-inch hydrophilic guidewires were used to create the subintimal channel. The tip of the wire was introduced into the subintimal channel to form a loop and advanced distally with support of a 4–5Fr catheter or a microcatheter

Table 1. Baseline Clinical Characteristics of Patients Undergoing Endovascular Treatment of Long Femoropopliteal Artery Occlusions

	Intraluminal approach (n=233)	Subintimal approach (n=228)	P value
Age (years)	69.9±10.1	70.2±9.0	0.773
Sex, male	184 (79.0)	188 (82.5)	0.406
Hypertension	167 (71.7)	170 (74.6)	0.553
Diabetes mellitus	111 (47.6)	114 (50.0)	0.679
Hypercholesterolemia	82 (35.2)	98 (43.0)	0.106
Chronic kidney disease	33 (14.2)	41 (18.0)	0.322
End-stage renal disease	16 (6.9)	21 (9.2)	0.451
Current smoker	93 (39.9)	73 (32.0)	0.095
Coronary artery disease	121 (51.9)	136 (59.6)	0.115
Stroke	31 (13.3)	44 (19.3)	0.106
Critical limb ischemia	81 (34.8)	69 (30.3)	0.351
Medications at hospital discharge			
Aspirin	200 (85.8)	191 (83.8)	0.626
Clopidogrel	196 (84.1)	184 (80.7)	0.400
Cilostazol	109 (46.8)	93 (40.8)	0.229
Dual-antiplatelet therapy	183 (75.0)	176 (72.4)	0.588
Triple-antiplatelet therapy	83 (34.0)	70 (28.8)	0.254
Statin	169 (72.5)	146 (64.0)	0.063

Dual-antiplatelet therapy: aspirin and clopidogrel. Triple-antiplatelet therapy: aspirin, clopidogrel, and cilostazol.

until the wire re-entered the true lumen at the distal stump. We considered wire passage to be subintimal when the tip of the advanced wire formed a loop and when linear or spiral dissections were visible at the proximal and distal stumps. In cases of difficult re-entry, a re-entry device (Outback Ltd., Cordis, Bridgewater, NJ, USA) was used to achieve wire passage into the true lumen. The Outback Re-entry catheter has been available in Korea since December 2009.

When antegrade passage of wires was not feasible, an additional retrograde approach was attempted through pedal or tibial artery puncture. After crossing the target lesion with wires, predilatation was routinely performed. Lesions with residual stenosis >30% or flow-limiting dissections after predilatation required stent implantation. Choice of self-expanding nitinol stents (SMART [Cordis]; Zilver [Cook, Bloomington, IN, USA]; Absolute Pro [Abbott Vascular, Redwood City, CA, USA]; Complete SE, [Medtronic, Santa Rosa, CA, USA]; or Protégé Everflex [Covidien, Plymouth, MN, USA]) was made at the operator's discretion. Deployed stents were routinely dilated with balloons for better apposition. After the procedure, patients routinely received aspirin (100 mg/day) lifelong and clopidogrel (75 mg/day) or cilostazol (200 mg/day) for at least 1 month. All patients were followed clinically at 1 month and every 3–6 months thereafter. Ankle-brachial index (ABI) was evaluated at 1-year intervals or if the symptom status deteriorated. At least 1 imaging study, such as CT angiography, duplex ultrasound, or intra-arterial angiography, was performed in the event of either a >0.15 decrement in the ABI or worsening symptoms that were reflected by changes in the Rutherford category.

Study Endpoints and Definitions

Primary endpoint was clinical primary patency at 1 year, which was defined as absence of significant restenosis (>50%) on imaging studies or symptom aggravation by Rutherford category with decrease in the ABI >0.15. Restenosis was defined by peak systolic velocity index (ratio of intrastenotic peak systolic velocity to prestenotic velocity) <2.4 by duplex ultrasound. The secondary endpoint was clinically driven TLR-free survival. TLR was defined as any surgical or percutaneous intervention at the target lesion after the index procedure. All clinically driven TLR was performed for restenotic lesions with both worsening symptoms and >0.15 decrease in the ABI. Poor run-off was defined as absence of patent (luminal stenosis <50%) infrapopliteal run-off vessels. Technical success was defined as recanalization of the target lesion in the absence of residual stenosis >30% or flow-limiting dissection. A major complication was defined as any event that was either fatal or required surgical management or rehospitalization within 30 days of the procedure.

Statistical Analysis

Continuous variables are presented as mean±standard deviation and were compared using Student's t-test for parametric data and the Mann-Whitney test for nonparametric data. Categorical variables are presented as number (percentage) and were compared using the chi-square test or Fisher›s exact test. Clinical primary patency and TLR-free survival were analyzed using Kaplan-Meier survival curves, and the log-rank test was used to compare outcomes between the patient groups. Univariate Cox proportional hazards regression analyses using baseline clinical, lesion, and procedural variables were performed to identify factors associated with restenosis. The variables achieving a P-value <0.10 in the univariate analysis and variables that are considered clinically important were evaluated in the multivariate analysis model to determine the independent predictors of restenosis. All statistical analyses were

Table 2. Lesion and Procedural Data of Patients Undergoing Endovascular Treatment of Long Femoropopliteal Artery Occlusions

	Intraluminal approach (n=244)	Subintimal approach (n=243)	P value
TASC			0.716
C	77 (31.6)	72 (29.6)	
D	167 (68.4)	171 (70.4)	
Total occlusion	244 (100.0)	243 (100.0)	0.964
Lesion length, mm	245.2±70.0	257.9±87.7	0.078
Stent implantation	154 (70.3)	178 (77.1)	0.129
No. of implanted stents	1.0±0.9	1.2±0.8	0.065
Stent diameter, mm	6.6±0.7	6.7±0.7	0.047
Stented length, mm	164.6±88.9	172.8±89.9	0.407
Stented length/lesion length ratio	0.5±0.8	0.6±0.8	0.513
Full-lesion stenting	53 (24.2)	62 (26.8)	0.594
Stent type			0.447
SMART	119 (77.3)	125 (70.2)	0.185
Complete SE	17 (11.0)	21 (11.8)	0.965
Zilver	4 (2.6)	4 (2.2)	1.000
Absolute Pro	10 (6.5)	18 (14.4)	0.325
Protégé Everflex	4 (2.6)	10 (5.6)	0.273
Poor distal run-off	33 (13.5)	34 (14.0)	0.986
Combined targets			
Iliac lesions	47 (19.3)	67 (27.5)	0.064
BTK lesions	50 (20.5)	61 (25.1)	0.269
Ankle-brachial index			
Preprocedure	0.5±0.2	0.5±0.2	0.192
Postprocedure	0.8±0.2	0.8±0.2	0.623
Technical success	219 (89.8)	231 (95.1)	0.041
Approach direction			0.969
Contralateral	195 (79.9)	192 (79.0)	
Ipsilateral	49 (20.1)	51 (21.0)	
Bidirectional approach	49 (20.1)	10 (4.1)	<0.001
Use of reentry device	0 (0)	30 (12.3)	<0.001
Directional atherectomy	5 (2.0)	3 (1.2)	0.726
Major complications	1 (0.4)	10 (4.1)	0.014
Bleeding	0 (0)	1 (0.4)	0.998
Access site complications	0 (0)	4 (1.6)	0.131
Distal embolization	0 (0)	4 (1.6)	0.131
Vascular rupture	1 (0.4)	1 (0.4)	>0.999
All complications	17 (7.0)	22 (9.1)	0.496
Bleeding	12 (4.9)	6 (2.1)	0.233
Access site complications	8 (3.3)	9 (3.7)	0.993
Distal embolization	2 (0.8)	4 (1.6)	0.678
Vascular rupture	4 (1.6)	7 (2.9)	0.537

BTK, below-the-knee; TASC, Inter-Society Consensus for the Management of Peripheral Arterial Disease.

performed using R version 3.3.2 (http://www.r-project.org/). P<0.05 was considered statistically significant.

Results

Baseline Clinical and Lesion Characteristics

There were no significant differences in the clinical characteristics of the 2 groups (**Table 1**), although the subintimal group tended to be prescribed statins less frequently (64.0%) than the intraluminal group (72.5%, P=0.063). There was no significant difference in the use of dual (aspirin and clopidogrel) or triple (aspirin, clopidogrel, and cilostazol) antiplatelet therapy. Lesion characteristics and procedural data of the treated patients are presented in **Table 2**. All lesions were chronic total occlusions (CTOs). TASC II D lesions were similarly present in both the subintimal and intraluminal groups (70.4% vs. 68.4%, P=0.716); however, the subintimal group showed a non-significant trend towards a longer lesion length (257.9±87.7 vs. 245.2±70.0 mm, P=0.078) and more frequent presence of combined iliac artery lesions (27.5% vs. 25.1%, P=0.064) than the intraluminal group. Infrapopliteal run-off,

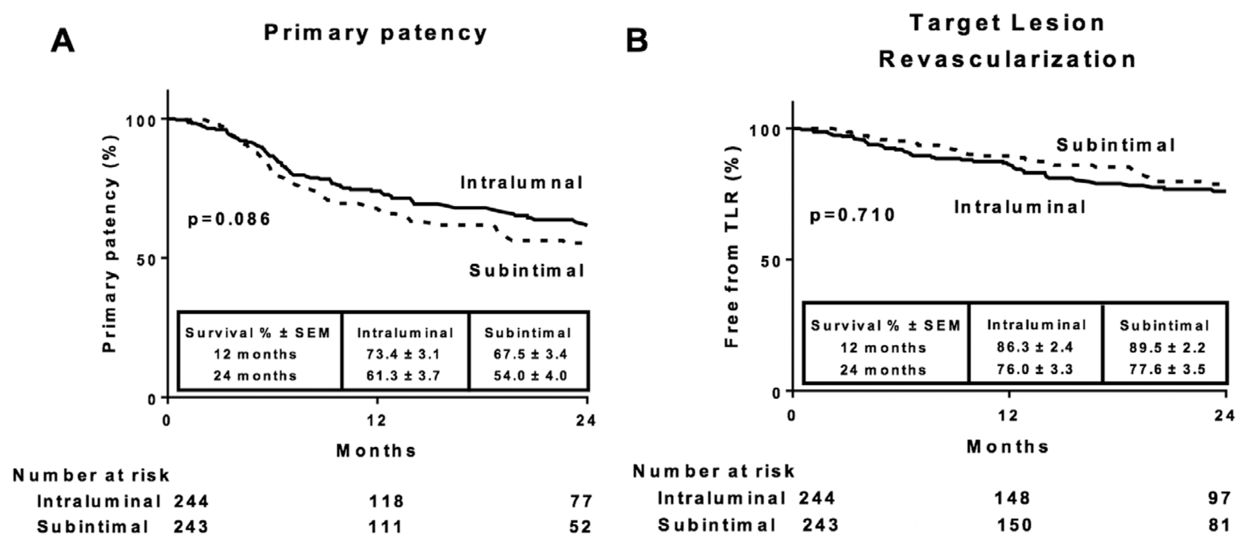

Figure 2. Kaplan-Meier curves for clinical primary patency (**A**) and target lesion revascularization-free survival (**B**) for the subintimal and intraluminal approaches for TASC II femoropopliteal occlusions. TASC, Inter-Society Consensus for the Management of Peripheral Arterial Disease.

concomitantly treated infrapopliteal lesions, and preprocedural ABIs were comparable between the 2 groups.

Immediate Procedural Outcomes

The technical success rate was higher in the subintimal group (95.1%) than in the intraluminal group (89.8%, P=0.041). An additional distal puncture for a bidirectional approach was performed in 20.1% of the intraluminal group and in 4.1% of the subintimal group (P<0.001). A re-entry device was used in 12.3% of the subintimal group. With adoption of additional retrograde approaches and use of re-entry devices, technical success was improved from 77.6% to 95.1% for the subintimal group and from 73.8% to 89.8% for the intraluminal group. Stent implantation was performed in 77.1% of the subintimal group patients and in 70.3% of the intraluminal group patients, showing no significant difference between groups (P=0.129). The number of stents (1.2±0.8 vs. 1.0±0.9, P=0.065) and the total stented length (172.8±89.9 vs. 164.6±88.9 mm, P=0.407) were comparable between the 2 groups. However, stent diameter was larger in the subintimal group (6.7±0.7 vs. 6.6±0.7, P=0.047). Periprocedural complication rates did not differ significantly between the 2 groups (9.1% vs. 7.0%, P=0.496); however, the incidence of major complication was higher in the subintimal group (4.1%) than in the intraluminal group (0.4%, P=0.014).

Mid-Term Outcomes

The mean follow-up duration was 22.1±20.4 months. The clinical primary patency rates did not differ significantly between groups. The subintimal group, however, showed a trend towards a lower primary patency rate than the intraluminal group (67.5 vs. 73.4% at 12 months and 54.0 vs. 61.3% at 24 months, P=0.086; **Figure 2A**). The clinically driven TLR-free survival was 89.5% and 77.6% in the subintimal group and 86.3% and 76.0% in the intraluminal group at 12 and 24 months, respectively, indicating no significant difference between the 2 groups at either time point (P=0.710; **Figure 2B**). In the Cox proportional hazard analysis, poor distal run-off (hazard ratio [HR] 2.59, 95% confidence interval [CI] 1.30–5.16, P=0.007), hypercholesterolemia (HR 1.63, 95% CI 1.19–2.23, P=0.002), lesion length per cm (HR 1.002, 95% CI 1.00–1.04, P=0.021), and stent length >150 mm (HR 1.42, 95% CI 1.03–1.99, P=0.034) were identified as independent risk factors for restenosis (**Table 3**). However, the subintimal approach was not independently associated with restenosis.

Discussion

To summarize, this study demonstrated that the subintimal approach yielded a higher technical success rate, but the patients in this group experienced more major complications than the intraluminal group. The clinical primary patency and clinically driven TLR-free survival did not differ significantly between the subintimal and intraluminal groups. Additionally, poor distal run-off, lesion length, stent length >150 mm, and hypercholesterolemia were identified as independent risk factors for restenosis.

Technical Success and Safety of Subintimal Approach

Since its first application in 1989,[3] the subintimal approach has shown improvement in its technical success rate.[2,7,12] London et al reported a technical success rate of 81% in occlusions of <10 cm; however, the success rate was only 68% in lesions >20 cm.[2] Adoption of an additional retrograde approach through distal pedal or tibial artery puncture and introduction of re-entry devices resulted in a remarkable improvement in the technical success rate of subintimal angioplasty in long CTO lesions.[5,7,9,12–14] Yilmaz et al reported an 88% success rate in long superficial femoral artery occlusion (mean length, 20.0 cm) with use of an retrograde approach in 82% of study participants.[14]

Table 3. Cox Proportional Hazard Regression Model for Restenosis After Endovascular Treatment of Long Femoropopliteal Artery Occlusions

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Subintimal approach	1.29	0.96–1.74	0.086	1.24	0.91–1.69	0.167
Age	1.00	0.99–1.02	0.871			
Female sex	1.36	0.95–1.94	0.089	1.35	0.94–1.93	0.109
Hypertension	0.99	0.71–1.39	0.976			
Diabetes mellitus	1.06	0.79–1.43	0.689			
Dyslipidemia	1.61	1.20–2.17	0.001	1.67	1.23–2.26	0.001
Chronic kidney disease	0.98	0.63–1.54	0.945			
End-stage renal disease	1.06	0.50–1.78	0.853			
Current smoker	1.01	0.75–1.37	0.927			
Coronary artery disease	0.79	0.59–1.06	0.111	0.72	0.53–0.98	0.035
Critical limb ischemia	1.05	0.75–1.46	0.791			
Aspirin	0.95	0.63–1.43	0.816			
Clopidogrel	1.16	0.76–1.75	0.495			
Cilostazol	0.84	0.62–1.13	0.251			
Dual-antiplatelet therapy	0.99	0.71–1.38	0.952			
Triple-antiplatelet therapy	0.94	0.68–1.29	0.697			
Statin	1.08	0.78–1.50	0.637			
Lesion length, mm	1.00	1.00–1.01	0.001	1.00	1.00–1.01	0.001
Stent implantation	1.11	0.77–1.61	0.578			
Stent diameter, mm	1.10	0.88–1.38	0.398			
Stent length, mm	1.00	0.99–1.00	0.183			
Stent-to-lesion length ratio >50%	1.17	0.86–1.59	0.322			
Full-lesion stenting	0.97	0.68–1.40	0.889			
Combined iliac lesion	0.82	0.86–1.71	0.260			
Combined BTK lesion	1.35	0.95–1.92	0.091	0.90	0.45–1.79	0.761
TASC II D	1.16	0.85–1.60	0.347			
Poor distal run-off	1.75	1.17–2.62	0.006	2.04	1.06–3.96	0.034
Re-entry device	1.10	0.88–1.38	0.398			

BTK, below-the-knee; CI, confidence interval; HR, hazard ratio; TASC, Inter-Society Consensus for the Management of Peripheral Arterial Disease.

Soga et al used a bidirectional approach in 37% of their subintimal angioplasty group and achieved technical success in 90% of these patients (mean occlusion length, 23.5 cm) even without use of a re-entry device.[13] Gandini et al obtained 100% success rate with the Outback Ltd re-entry catheter in TASC II D femoropopliteal artery disease compared with only a 42.3% success rate with a manual re-entry method.[7] In our study, we also achieved a high technical success rate (95.1%) in long CTO lesions with use of a combined retrograde approach (4.1%) and re-entry device (12.3%) with the subintimal method.

In this study, the technical success rate of the subintimal approach was higher than that of the intraluminal approach. Our previous single-center study also showed a tendency of higher technical success rates with the subintimal approach (95.1%) than with the intraluminal approach (86.7%, P=0.11) among 121 individuals.[15] Soga et al[13] reported similar technical success rates for the intraluminal (91%) and subintimal (90%) approaches based on intention-to-treat analysis; however, in their study, 25% of the intraluminal approach cases crossed over to become subintimal approach cases after difficulty with intraluminal angioplasty. Thus, the subintimal approach appears to achieve a higher technical success rate than intraluminal angioplasty.

On the other hand, the major complication rate was higher for the subintimal approach group than the intraluminal approach group in that study.[13] Most of the major complications in the subintimal group were access site complications and distal embolizations. In our opinion, the access site complications may not be directly related to the subintimal approach. Inclusion of thrombotic lesions may have been the reason for increased distal embolization requiring surgical interventions in the subintimal group. Previous studies reported no significant difference in complications rates between the subintimal and intraluminal groups.[12,16] As the major complication rates of subintimal angioplasty in the previous studies varied from 0% to 13%,[7,12,15,16] the periprocedural complication rates (4.1% for major complicates and 9.1% for all complications) observed in this study appear to be still rather low.

Patency After Subintimal Angioplasty

The 1-year patency rates for the subintimal approach for long CTO lesion of ≥20 cm in early studies ranged from 22% to 56%.[2,13,17] With the introduction of self-expanding stents, however, the patency rate of the subintimal approach improved remarkably.[9,12,15,17–19] In a meta-analysis of 37 studies, the 12-month primary patency rate was found to be 47.9% for the subintimal approach without implantation of stents, 61.6% for the subintimal approach with provisional stenting, and 69.2% for the subintimal approach with primary stenting.[17] In our study, adoption of different stenting strategies depending on the operator resulted in a primary patency rate in the subintimal group of 67.5% at 1 year and 54.0% at 2 years, consistent with previous studies. These primary patency rates were also similar to those observed for the Japanese registry, as reported by Soga et al;[13] however, in contrast to the Japanese registry results, spot stenting rather than long stenting was preferentially performed in our study. Long stenting or 'full-metal jacket' stenting has been reported to be associated with increased risk of restenosis in previous studies,[5,19] but because of the unavailability of detailed procedural data from the Japanese registry study, it is difficult to compare the data from the 2 registries.

To date, no randomized controlled trial directly comparing subintimal angioplasty vs. intraluminal angioplasty for femoropopliteal artery disease has been published; however, several retrospective studies demonstrated no significant difference between the 2 wire-crossing techniques in terms of primary patency or TLR-free survival.[12,15,20] In the present study, the subintimal approach showed a trend towards lower primary patency compared with the intraluminal approach. However, the subintimal approach was not associated with restenosis in the Cox proportional hazard multivariate analysis model after adjustment for confounding factors. Thus, the wire-crossing technique (i.e., subintimal or intraluminal) does not seem to have an effect on the mid-term patency. In agreement with previous studies, poor distal run-off, lesion length, stent length >150 mm, and hypercholesterolemia were identified as independent risk factors for restenosis in this study.[5,19,21,22,23]

Study Limitations

First, this was a retrospective study with the inherent limitations involved in retrospective studies involving electronic medical records. Second, subintimal or intraluminal passage of the wires was not confirmed by intravascular ultrasound during the procedure. Thus, we used the term "subintimal approach" instead of "subintimal angioplasty." Third, differences in procedural skills and strategies of the operators could not be considered because of the limited study population. Fourth, during the 10 years that procedures were performed, there might have been changes in technique of procedures and choice of stents. However, the present study did not include cases of treatment with interwoven nitinol stents or drug-eluting technologies that might have affected the primary patency. In the choice of stents, there was no significant difference between the intraluminal and subintimal groups. Fifth, there was no information on the severity of calcification in the target lesion. Heavily calcified lesions are often challenging for endovascular procedures and affect the treatment strategy. However, currently, there is no established consensus on how to define the severity of calcification.

Conclusions

In complex femoropopliteal occlusive lesions, the subintimal approach achieved a higher technical success rates as well as similar mid-term primary patency and TLR-free survival rates compared with the intraluminal approach.

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Supplementary Files

Supplementary File 1

Appendix S1. K-VIS Investigators

Please find supplementary file(s);
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