

# Effect of Target Lesion Revascularization on Restenosis Lesions of the Superficial Femoral Artery without Recurred Symptoms after Endovascular Therapy

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**Aim:** This study aims to elucidate the effects of early application of target lesion revascularization (TLR) to restenosis lesions of the superficial femoral artery (SFA) without recurrence of symptoms. Despite recent improvements in endovascular therapy (EVT) for the SFA, restenosis remains to be a problem. However, restenosis is not always associated with the recurrence of limb symptoms. Although early application of TLR is not generally approved for restenosis lesions of the SFA without recurred symptoms, it is expected to contribute to long-term patency and other favorable outcomes. Nonetheless, its effectiveness remains to be determined.

**Methods:** We retrospectively analyzed 616 patients who developed restenosis after undergoing femoro-popliteal EVT for claudication (Rutherford category 1 to 3) due to *de novo* femoro-popliteal lesions between January 2010 and December 2016 at 11 centers in Japan. Recurred symptoms were defined as symptoms of the same or higher Rutherford categories than those immediately before the initial EVT.

**Results:** Of the patients, 291 (47 %) lacked recurred symptoms; 69 (24 %) underwent TLR for restenosis. After propensity matching, the risk of occlusion was determined to be not significantly different between the TLR and observation groups; the 3-year occlusion-free rate was 68 % and 62 %, respectively ( $P=0.84$ ). The risk of recurring symptoms, critical limb ischemia, and all-cause death was also found to be comparable between groups. The incidence of target vessel revascularization was significantly higher in the TLR than in the observation group (1.55 [95 % confidence interval: 1.25–1.93] vs. 0.59 [0.41–0.85] per 3 person-years).

**Conclusions:** In patients with SFA restenosis without recurred symptoms, early application of TLR showed no advantages.

**Key words:** Superficial femoral artery, Target lesion revascularization, Without symptom

**Abbreviations:** ABI = ankle-brachial index, CLI = critical limb ischemia, DCB = drug-coated balloon, EVT = endovascular therapy, PSVR = peak systolic velocity ratio, SFA = superficial femoral artery, TLR = target lesion revascularization

## Introduction

The procedures of revascularization for peripheral artery disease include bypass graft surgery and endovascular therapy (EVT). However, the indications of EVT have gradually expanded in recent years<sup>1-3</sup>). In principle, EVT is approved only for symptomatic patients, and the most important symptom is intermittent claudication<sup>2</sup>). In the treatment of claudication in the iliac artery region, favorable outcomes have been achieved using stent placement<sup>4, 5</sup>). However, for claudication of the superficial femoral artery (SFA), which is the site most likely to be targeted for treatment, a high restenosis rate was determined to be a problem despite the recent advances in devices<sup>3, 6-9</sup>).

When restenosis, particularly in-stent restenosis, occurs, the consequent therapeutic outcomes are markedly poor, and the subsequently applicable therapeutic strategies are limited<sup>10-12</sup>). In case of in-stent restenosis, as the severity of restenosis or reocclusion is worse, the consequent therapeutic outcomes are poorer<sup>11</sup>). There were several reports that despite close duplex surveillance and re-intervention, effect on the prognosis remained to be poor, and there was no significant difference between follow-up only of symptoms<sup>13, 14</sup>). Due to the rapid deterioration of restenosis lesions, the treatment for SFA restenosis remains challenging, as the timing of intervention for restenosis has not been investigated. Re-intervening early before symptom recurrence may prevent reocclusion, and consequently, maintain the patency of the treated vessel; however, this possibility has not been investigated.

Generally, restenosis is diagnosed using noninvasive methods such as ankle-brachial index (ABI) determination and duplex ultrasound imaging. Although restenosis is diagnosed using these tests, it is not always associated with the recurrence of symptom. In studies contributing to the approval of SFA stenting, clinical studies on drug-coated balloons (DCBs), and other related studies, restenosis has been defined as a peak systolic velocity ratio (PSVR) of 2.4 or higher as assessed using duplex ultrasound<sup>6, 15, 16</sup>). However, at this degree of restenosis, blood flow is maintained in the lower limbs; thus, lower-limb symptoms may not be detectable or not as severe as those at the initial treatment. Although EVT is generally not considered to be indicated for asymptomatic patients, no evidence has been found on early intervention for restenosis lesions before the onset of symptoms.

In patients undergoing femoro-popliteal bypass grafting in the SFA, follow-up with duplex ultrasound and other examinations is recommended<sup>17</sup>). When restenosis occurs, early intervention is recommended, regardless of the presence or absence of symptoms<sup>18, 19</sup>). The objective of early intervention is to maintain the patency of the bypass. Meanwhile, early intervention is also expected to exert similar effects after EVT for SFA.

However, at present, there is no evidence on the effects of early intervention for restenosis lesions of the SFA without recurring symptoms, and the clinical significance of early intervention remains unclear.

## Aims

This study aims to determine whether early TLR is effective for restenosis lesions of the SFA without recurring symptoms.

## Methods

### Study Design

This was a retrospective, multicenter clinical investigation aimed at analyzing the effect of TLR on restenosis lesions of the SFA without recurring symptoms after EVT. The primary outcomes of this study were set as follows: (1) avoidance of vascular occlusion, (2) recurrence of symptoms, (3) progression to CLI, and (4) all deaths. The main inclusion criterion was first restenosis detected after femoro-popliteal EVT for claudication (Rutherford category 1 to 3) due to *de novo* femoro-popliteal lesions between January 2010 and December 2016 at 11 centers in Japan. Cases that treated using a DCB or an atherectomy device were excluded. The institutional review boards of the participating institutions approved the study, which was conducted in accordance with the Declaration of Helsinki. The current study was exempt from informed consent because it was a retrospective research work using existing medical records; in fact, relevant information about the study is openly available to the public in accordance with the ethical guidelines for medical and health research involving human subjects.

### Patient Population

In accordance with the inclusion criterion, this analysis has included 616 patients (mean age 73 ± 9

years, 66 % men), in whom restenosis was detected after undergoing femoro-popliteal EVT for claudication. Restenosis was defined as a PSVR of 2.4 or higher as assessed using duplex ultrasound. Recurred symptoms were defined as symptoms of the same or more severe Rutherford categories than those immediately before the initial EVT.

### Procedural Protocol

The selection of drug and exercise therapies at the time of the initial EVT and TLR, as well as during follow-up, was left to the discretion of each operator at each institution. The selection of the strategies for initial EVT was also left to the discretion of each operator at each institution. For the initial EVT, stents were used in 75 % of the patients, while full lesion coverage treatment with stents was used in 59 %. In this retrospective study, we did not enroll any patient for whom a DCB, an atherectomy device, or a stent graft had been used. The success of the initial EVT was defined as residual stenosis of <30 %, and successfully treated patients were followed up according to the protocol of each institution. Symptoms, ABI, and duplex ultrasound images were assessed regularly to determine the presence or absence of restenosis. Thereafter, the patients were followed up yearly for clinical symptoms.

When restenosis was first detected, patients became eligible for the current study. At that time, the morphology and severity of restenosis were assessed using duplex ultrasound or angiography with computed tomography, magnetic resonance imaging, or catheterization. The decision on whether to perform TLR in patients diagnosed as having restenosis regardless of symptomatic or asymptomatic status was left to the discretion of each operator at each institution. In many patients without recurred symptoms, TLR was not performed, but they were placed under follow-up observation. However, in some patients, TLR was performed with their consent because of the risk of reocclusion, treatment difficulty in case of reocclusion, and concerns about future recurrence or aggravation of symptoms (including progression to critical limb ischemia [CLI]).

The patients were divided into two groups: the TLR group, which included patients for whom TLR was planned immediately after the diagnosis of the first restenosis and performed within the following 2 months, and the observation group, which included those who were first placed under clinical follow-up observation. Restenosis was then classified into the following five patterns: type 1, “focal” pattern, which may be “edge proximal” or “edge distal” depending on the location; type 2, “multifocal” pattern, which may

also exhibit edge restenosis but may also be “edge bilateral”; type 3, “moderate” pattern; type 4, “diffuse” pattern; and type 5, “occlusion.” This classification, proposed by Dr. Garcia<sup>20</sup>, was used because it allowed us to classify restenosis occurring after balloon angioplasty or stenting in the same manner.

### Statistical Analysis

Data are presented as the mean  $\pm$  standard deviation or median (interquartile range) for continuous variables and number (percentage) for categorical variables, if not otherwise mentioned.  $P < 0.05$  was considered statistically significant, and 95 % confidence intervals are reported when appropriate. We first extracted patients without recurred symptoms at the time of restenosis detection; we then compared their clinical characteristics with those of patients with recurred symptoms. Thereafter, we divided the population without recurred symptoms into patients who underwent TLR within 2 months (TLR group) and those who did not (observation group). The differences in baseline characteristics between groups were crudely tested using Welch's  $t$ -test for continuous variables including age, body mass index, and ABI; Fisher's exact test for dichotomous variables; and the Mann-Whitney  $U$ -test for other continuous variables and ordinal categorical variables.

When clinical outcomes were compared between the TLR and observation groups, propensity score matching was performed in order to minimize intergroup differences in baseline characteristics. The propensity score was then developed using a logistic regression model including the following explanatory variables: months after the initial EVT, sex, age, body mass index, ambulatory status, smoking, diabetes mellitus, renal function, coronary artery disease, antiplatelet agent use, Rutherford classification, ABI, lesion severity, and stent use at the initial EVT. Matching (1:1) was performed on the logit of the propensity score within the caliper of 0.2 standard deviation of the logit of the propensity score. After matching, the intergroup comparison results were analyzed using paired analysis, including paired  $t$ -test for continuous variables, McNemar's test for dichotomous variables, and Wilcoxon signed-rank test for ordinal categorical variables. Time-to-event outcomes were analyzed using the Kaplan-Meier method and stratified log-rank test, except for target vessel revascularization, which was analyzed using the generalized linear mixed model with a Poisson distribution and log link function. The interaction effect of baseline characteristics was assessed using the stratified Cox proportional hazards regression model with stratification on the quintiles of the propensity score.

**Table 1.** Baseline characteristics of overall study population

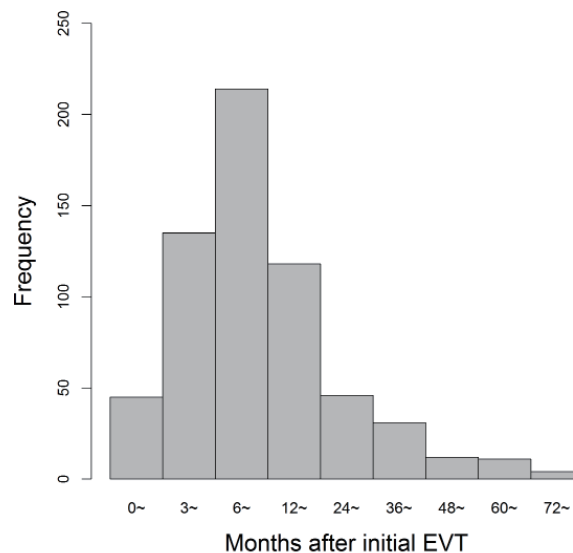
<i>n</i>	616	<i>n</i>	616
<b>At detection of restenosis</b>		<b>At initial EVT</b>	
Male sex	66%	Preoperative Rutherford classification	
Age (years)	73 ± 9	Category 1	1%
BMI (kg/m <sup>2</sup> )	22.7 ± 3.7	Category 2	21%
Non-ambulatory status	9%	Category 3	78%
Smoking		Preoperative ABI	0.59 ± 0.21
Never	44%	Data unavailable	1%
Past	32%	History of aortoiliac revascularization	35%
Current	24%	TASC II classification	
Hypertension	90%	Class A	22%
Dyslipidemia	59%	Class B	28%
Diabetes mellitus	62%	Class C	24%
Renal function		Class D	26%
eGFR ≥ 30	58%	Chronic total occlusion	51%
eGFR < 30	16%	PACSS classification	
On dialysis	25%	Grade 0	26%
Coronary artery disease	54%	Grade 1	22%
Cerebrovascular disease	25%	Grade 2	24%
Aspirin use	91%	Grade 3	10%
Thienopyridine use	70%	Grade 4	19%
Cilostazol use	27%	Stent use at initial EVT	
Rutherford classification		Full coverage	59%
Category 0	13%	None	25%
Category 1	16%	Spot stenting	15%
Category 2	27%	Infrapopliteal runoff	
Category 3	37%	No runoff	7%
Category 4	4%	1 runoff	36%
Category 5	4%	2 runoffs	41%
ABI	0.65 ± 0.24	3 runoffs	15%
Data unavailable	1%	Data unavailable	1%
Restenotic pattern		Postoperative Rutherford classification	
Type I	31%	Category 0	43%
Type II	17%	Category 1	49%
Type III	16%	Category 2	8%
Type IV	16%	Category 3	1%
Type V	21%	Postoperative ABI	0.90 ± 0.16
		Data unavailable	1%

All statistical analyses were performed using R version 3.1.0 (R Development Core Team, Vienna, Austria).

### Results

The baseline characteristics of the study population are summarized in **Table 1**. The mean patient age was 73 ± 9 years, and 66 % of the patients were men. Restenosis pattern type 5 (i.e., occlusive lesion) accounted for 21 % of the restenosis cases, whereas chronic total occlusion was found in 51 % at the initial EVT. As presented in **Fig. 1**, restenosis was detected within 1 year after the initial EVT in most patients. The median duration between the initial EVT and restenosis detection was 9 (6–15) months.

A total of 291 patients (47 %) lacked recurred symptoms; the 95% confidence interval of the prevalence was calculated to be 43–51 %. **Table 2** demon-



**Fig. 1.** Histogram of month after initial EVT (i.e., duration between initial EVT and detection of restenosis)

**Table 2.** Comparison of baseline characteristics between patients with and without recurred symptoms

	Patients without recurred symptoms (n=291)	Patients with recurred symptoms (n=325)	P value		Patients without recurred symptoms (n=291)	Patients with recurred symptoms (n=325)	P value
<b>At detection of restenosis</b>				<b>At initial EVT</b>			
Month after initial EVT	9 (6 - 16)	8 (6 - 15)	0.40	Preoperative Rutherford classification			0.003
Month after patency last confirmed	4 (3 - 6)	4 (2 - 6)	0.19	Category 1	0%	1%	
Data unavailable	1%	2%	0.35	Category 2	16%	25%	
Male sex	64%	67%	0.40	Category 3	84%	74%	
Age (years)	74 ± 8	72 ± 9	0.048	Preoperative ABI	0.59 ± 0.21	0.60 ± 0.22	0.78
BMI (kg/m <sup>2</sup> )	22.9 ± 3.7	22.5 ± 3.6	0.17	Data unavailable	1%	1%	0.69
Non-ambulatory status	9%	10%	0.78	History of aortoiliac revascularization	38%	31%	0.062
Smoking			0.003	TASC II classification			0.064
Never	49%	39%		Class A	18%	25%	
Past	32%	32%		Class B	26%	30%	
Current	19%	29%		Class C	31%	17%	
Hypertension	92%	89%	0.28	Class D	25%	27%	
Dyslipidemia	61%	57%	0.29	Chronic total occlusion	53%	50%	0.47
Diabetes mellitus	64%	60%	0.41	PACSS classification			0.96
Renal function			0.85	Grade 0	27%	25%	
eGFR ≥ 30	57%	60%		Grade 1	20%	23%	
eGFR < 30	20%	13%		Grade 2	24%	23%	
On dialysis	23%	27%		Grade 3	10%	10%	
Coronary artery disease	58%	51%	0.11	Grade 4	19%	19%	
Cerebrovascular disease	28%	23%	0.19	Stent use at initial EVT			0.16
Aspirin use	90%	91%	0.49	None	22%	28%	
Thienopyridine use	75%	66%	0.014	Spot stenting	16%	14%	
Cilostazol use	29%	26%	0.59	Full coverage	62%	57%	
Rutherford classification			< 0.001	Infrapopliteal runoff			0.032
Category 0	27%	0%		No runoff	5%	10%	
Category 1	32%	1%		1 runoff	34%	39%	
Category 2	41%	16%		2 runoffs	47%	36%	
Category 3	0%	70%		3 runoffs	15%	15%	
Category 4	0%	7%		Data unavailable	1%	0%	0.35
Category 5	0%	7%		Postoperative Rutherford classification			0.88
ABI	0.72 ± 0.22	0.58 ± 0.24	< 0.001	Category 0	44%	42%	
Data unavailable	1%	1%	0.69	Category 1	46%	51%	
Restenotic pattern			< 0.001	Category 2	10%	6%	
Type I	41%	21%		Category 3	0%	1%	
Type II	23%	12%		Postoperative ABI	0.91 ± 0.14	0.89 ± 0.17	0.069
Type III	13%	18%		Data unavailable	1%	2%	0.18
Type IV	11%	21%					
Type V	12%	29%					

strates the differences of the clinical characteristics between patients with and without recurred symptoms. Compared with patients with recurred symptoms, those without recurred symptoms were determined to be older, were less likely to be smokers, were more frequently thienopyridine users, presented

milder restenotic lesions with higher ABI levels, and had more infrapopliteal runoffs.

Of the 291 patients without recurred symptoms, 69 (24 %) have undergone TLR for restenosis. TLR was successful in all cases. Compared with the observation group, the TLR group had a higher prevalence



of coronary artery disease and was more likely to have complaints of claudication (Table 3). The propensity score matching extracted a total of 61 pairs. After the matching, there was no remarkable intergroup difference in baseline characteristics (Table 3). Similarly, there was no difference in aspirin, thienopyridine, or cilostazol use after restenosis detection between the TLR and observation groups (85 % vs. 92 % [ $P=0.42$ ], 62 % vs. 67 % [ $P=0.69$ ], and 23 % vs. 26 % [ $P=0.83$ ]). The mean follow-up period after restenosis detection was  $2.5 \pm 1.6$  years.

As shown in Fig. 2A, the risk of occlusion was not significantly different between the TLR and observation groups; the 3-year occlusion-free rate was 68 % and 62 %, respectively ( $P=0.84$ ). Furthermore, the risk of recurring symptoms, CLI development, and all-cause death was also comparable between the two groups (Figs. 2B–D). None of the patients underwent bypass conversion or major amputation. The incidence of target vessel revascularization was significantly higher in the TLR group than in the observation group (1.55 [95 % confidence interval: 1.25–1.93] vs. 0.59 [0.41–0.85] per 3 person-years) (Fig. 3). Note that all the target vessel revascularization was TLR.

Finally, we examined the interaction effect of baseline characteristics on the association between TLR and the primary outcome. Consequently, as shown in Table 4, the Rutherford classification at restenosis detection had a significant interaction effect on the association. The hazard ratio of TLR vs. observation for arterial occlusion was 5.44 (95 % confidence interval 1.42–20.9) for Rutherford category 0, 1.18 (0.42–3.32) for Rutherford category 1, and 0.59 [0.29–1.20] for Rutherford category 2 ( $P$  for interaction = 0.008).

## Discussion

In patients without recurred symptoms, our findings did not reveal any clinical significance of performing TLR soon after restenosis occurred following EVT for claudication of the SFA. In the comparison between patients with and without recurred symptoms, those without recurred symptoms were determined to have morphologically milder restenosis and a significantly higher ABI at restenosis detection. Thus, symptomatic recurrence may be partially explained by the stenotic severity at restenosis detection. Given that restenosis is also progressive, restenosis even without recurring symptoms at the first detection may eventually progress to the level causing symptoms. Even in such a case, it is sufficient to consider TLR after symptomatic recurrence. In contrast,

when TLR is performed for restenosis without recurring symptoms, the procedure may simply be applied to physiologically insignificant stenosis that does not require any intervention even on a long-term basis. In addition, observational research on the natural course of stenosis after EVT detected by duplex reported that 39 % of stenotic lesions were stabilized<sup>21</sup>). From this study, even a restenosis lesion found without symptom recurrence may not necessarily require treatment also in the future.

Although a PSVR of 2.4 or higher, a criterion for monitoring after EVT for the SFA, is recognized as a criterion for the assessment of stent performance, it is not a universal criterion for all patients and has been found to be slightly strict for some patients.

After the performance of femoro-popliteal bypass grafting, intervention for restenosis before symptomatic recurrence has been recommended to maintain patency. The current study investigated whether TLR had clinical significance for the treatment of restenosis without recurring symptoms after conventional EVT. As a result, no clinical significance was found concerning maintenance of secondary patency, prevention of future symptomatic recurrence, and prevention of events that were caused by symptomatic aggravation and led to CLI. Although we have assumed that early intervention might prevent repetitive application of TLR for a long period and eventually reduce the frequency of TLR, the procedure was significantly more frequently performed in the TLR group than in the observation group. Because the frequency differed by only the first session of TLR performed in the early stages, early application of TLR was determined to have no advantage in terms of the frequency of subsequent intervention. This also suggests that early intervention is unlikely to have clinical significance.

Several studies have revealed that treatment with DCB achieves better therapeutic outcomes for in-stent restenosis than conventional treatment<sup>22–26</sup>). In the future, the demand for DCB will presumably increase in the treatment of restenosis of the SFA. In the current study, DCB had not been used for either initial EVT or TLR because when this study was designed, DCB was not approved in Japan. Although TLR was performed using balloon angioplasty or with a bare nitinol stent or drug-eluting stent based on the discretion of the operators, this study did not reveal any need for TLR for restenosis without recurring symptoms. With no data collected on the treatment content of TLR, it is difficult to say in this study whether the prognosis differs depending on the TLR strategy. If the use of DCB had improved the outcomes of TLR, then the clinical outcomes might have been better in patients undergoing the procedure than in those

**Table 3.** Baseline characteristics of patients with and without TLR for restenosis not accompanied by recurred symptoms

	Before matching			After matching		
	TLR group (n = 69)	Observation group (n = 222)	P value	TLR group n = 61)	Observation group (n = 61)	P value
<b>At detection of restenosis</b>						
Month after initial EVT	10 (5 - 17)	9 (6 - 15)	0.65	10 (5 - 17)	9 (6 - 15)	0.79
Month after patency last confirmed	4 (3 - 6)	4 (2 - 6)	0.71	4 (3 - 6)	3 (2 - 6)	0.95
Data unavailable	1%	1%	0.56	2%	0%	0.50
Male sex	57%	66%	0.15	56%	57%	1.00
Age (years)	74 ± 8	74 ± 9	0.69	75 ± 8	74 ± 8	0.78
BMI (kg/m <sup>2</sup> )	23.0 ± 3.5	22.9 ± 3.7	0.71	23.0 ± 3.6	23.4 ± 3.7	0.54
Non-ambulatory status	7%	9%	0.81	8%	8%	1.00
Smoking			0.88			0.42
Never	51%	48%		49%	44%	
Past	29%	33%		31%	26%	
Current	20%	18%		20%	30%	
Hypertension	93%	91%	1.00	92%	95%	0.68
Dyslipidemia	61%	61%	1.00	59%	62%	0.87
Diabetes mellitus	71%	61%	0.15	67%	59%	0.44
Renal function			0.85			0.60
eGFR ≥ 30	58%	56%		56%	51%	
eGFR < 30	19%	20%		20%	23%	
On dialysis	23%	23%		25%	26%	
Coronary artery disease	72%	53%	0.005	70%	66%	0.70
Cerebrovascular disease	29%	27%	0.88	30%	26%	0.86
Aspirin use	94%	88%	0.18	93%	90%	0.72
Thienopyridine use	81%	73%	0.20	82%	79%	0.83
Cilostazol use	23%	30%	0.29	23%	26%	0.84
Rutherford classification			< 0.001			0.62
Category 0	7%	33%		8%	11%	
Category 1	23%	35%		26%	25%	
Category 2	70%	32%		66%	64%	
ABI	0.68 ± 0.22	0.73 ± 0.22	0.067	0.69 ± 0.20	0.68 ± 0.21	0.77
Data unavailable	0%	1%	1.00	0%	0%	0.50
Restenotic pattern			0.085			0.69
Type I	32%	44%		33%	36%	
Type II	23%	23%		25%	18%	
Type III	19%	12%		16%	15%	
Type IV	12%	10%		11%	15%	
Type V	14%	12%		15%	16%	
<b>At initial EVT</b>						
Preoperative Rutherford classification			1.00			0.81
Category 1	0%	0%		0%	0%	
Category 2	16%	17%		18%	15%	
Category 3	84%	83%		82%	85%	
Preoperative ABI	0.62 ± 0.17	0.58 ± 0.22	0.18	0.62 ± 0.16	0.61 ± 0.21	0.80
Data unavailable	0%	1%	1.00	0%	0%	0.50
History of aortoiliac revascularization	33%	40%	0.33	34%	41%	0.57
TASC II classification			0.71			0.79
Class A	14%	19%		15%	18%	
Class B	26%	26%		28%	26%	
Class C	41%	28%		39%	36%	
Class D	17%	27%		18%	20%	

(Cont. Table 3)

	Before matching			After matching		
	TLR group (n = 69)	Observation group (n = 222)	P value	TLR group n = 61)	Observation group (n = 61)	P value
Chronic total occlusion	54%	52%	0.89	51%	46%	0.73
PACSS classification			0.78			0.39
Grade 0	22%	28%		23%	33%	
Grade 1	26%	18%		21%	18%	
Grade 2	25%	24%		25%	23%	
Grade 3	9%	11%		10%	8%	
Grade 4	19%	18%		21%	18%	
Stent use at initial EVT			0.93			0.84
None	20%	22%		21%	20%	
Spot stenting	16%	17%		18%	15%	
Full coverage	64%	61%		61%	66%	
Infrapopliteal runoff			0.78			0.77
No runoff	1%	5%		2%	2%	
1 runoff	36%	33%		38%	38%	
2 runoffs	48%	46%		48%	51%	
3 runoffs	14%	15%		13%	10%	
Data unavailable	0%	1%	1.00	0%	0%	0.50
Postoperative Rutherford classification			0.25			0.62
Category 0	33%	47%		34%	39%	
Category 1	62%	41%		62%	57%	
Category 2	3%	12%		3%	3%	
Category 3	1%	0%		0%	0%	
Postoperative ABI	0.92 ± 0.14	0.91 ± 0.14	0.82	0.91 ± 0.14	0.93 ± 0.15	0.45
Data unavailable	0%	1%	1.00	0%	0%	0.50

placed under follow-up observation. However, the current study could not confirm this assumption.

In the current study, symptomatic recurrence was defined as the onset of symptoms that were as severe as those at the initial EVT. For example, when symptoms were classified as Rutherford category 3 at the initial EVT and category 2 at restenosis detection, patients were determined to have no recurring symptoms despite being symptomatic. In other words, the “absence of symptomatic recurrence” does not mean “being asymptomatic.” In the current study, interaction effects were assessed to identify patients without recurred symptoms who would benefit from TLR. Although interaction effects on the risk of vascular occlusion were assessed, the application of TLR to patients without recurred symptoms did not reduce the incidence of occlusion in any subgroups. We assumed that TLR might be beneficial to patients with symptoms classified as Rutherford category 2 at restenosis detection, in other words, those with claudication symptoms that were milder than the symptoms before the initial EVT. However, no statistically significant benefit was observed. On the contrary, in asymp-

tomatic patients in Rutherford category 0 at restenosis detection, the application of TLR has increased the risk of vascular occlusion with a statistically significant difference. Thus, the application of TLR to asymptomatic patients is not beneficial. Instead, it is associated with the risk of vascular occlusion and may be harmful. TLR was found to be unacceptable.

### Limitations

This study shares the limitations of all retrospective, nonrandomized investigations, including the presence of a selection bias. Decisions on the strategies for the initial EVT, on whether to perform TLR at restenosis detection, and on the TLR procedures were left to the discretion of the attending physicians and operators.

The methods of drug and exercise therapies were determined to vary.

Because of the retrospective study design, there was a difference in the quality and frequency of duplex scanning between each institution.

The presence or absence of symptomatic recur-



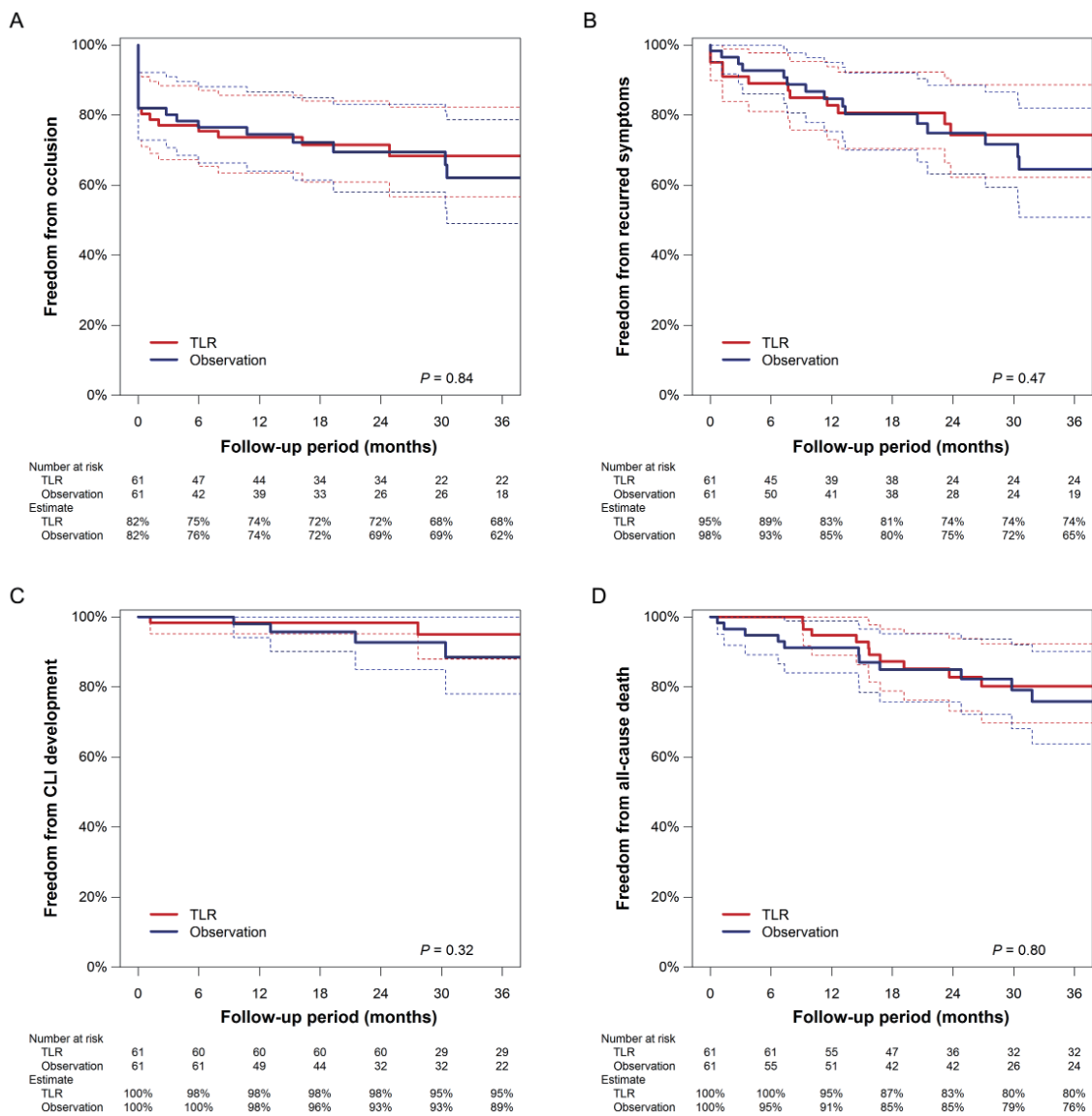


Fig. 2. Kaplan-Meier estimates of freedom rate from occlusion (A), recurred symptoms (B), CLI development (C), and all-cause death (D) after the detection of restenosis

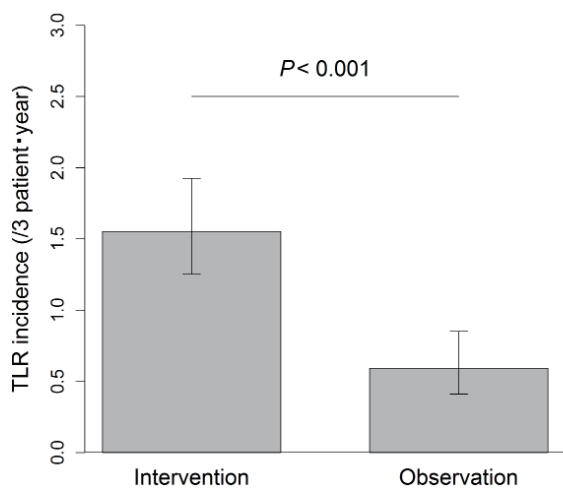


Fig. 3. Incidence of target vessel revascularization after the detection of restenosis

Error bars indicates 95 % confidence intervals.

**Table 4.** Interaction effect of baseline characteristics on the association between TLR and occlusion risk

	<i>n</i>	Hazard ratio [95% confidence interval] of TLR vs. Observation for arterial occlusion	<i>P</i> for interaction
Overall population	291	0.90 [0.52, 1.56] ( <i>P</i> =0.70)	
Month ater initial EVT			0.54
< 9 months	140	0.78 [0.36, 1.68] ( <i>P</i> =0.52)	
≥ 9 months	151	1.07 [0.48, 2.39] ( <i>P</i> =0.86)	
Month after patency last confirmed			0.90
< 4 months	142	0.96 [0.45, 2.05] ( <i>P</i> =0.92)	
≥ 4 months	146	0.90 [0.40, 2.01] ( <i>P</i> =0.80)	
Sex			0.30
Female	105	0.68 [0.31, 1.51] ( <i>P</i> =0.34)	
Male	186	1.16 [0.54, 2.47] ( <i>P</i> =0.71)	
Age			0.78
< 74 years	126	0.83 [0.31, 2.19] ( <i>P</i> =0.70)	
≥ 74 years	165	0.97 [0.49, 1.90] ( <i>P</i> =0.92)	
Body mass index			0.57
< 22.6 kg/m <sup>2</sup>	132	0.75 [0.33, 1.71] ( <i>P</i> =0.49)	
≥ 22.6 kg/m <sup>2</sup>	159	1.00 [0.48, 2.10] ( <i>P</i> =0.99)	
Ambulatory status			0.40
Ambulatory	265	0.84 [0.45, 1.58] ( <i>P</i> =0.59)	
Non-ambulatory	26	1.57 [0.39, 6.32] ( <i>P</i> =0.52)	
Smoking			0.25
Never	142	0.58 [0.25, 1.36] ( <i>P</i> =0.21)	
Past	94	1.43 [0.61, 3.33] ( <i>P</i> =0.41)	
Current	55	1.05 [0.31, 3.58] ( <i>P</i> =0.94)	
Hypertension			0.63
No	24	0.54 [0.06, 4.74] ( <i>P</i> =0.57)	
Yes	267	0.93 [0.51, 1.71] ( <i>P</i> =0.81)	
Dyslipidemia			0.15
No	113	0.51 [0.19, 1.40] ( <i>P</i> =0.19)	
Yes	178	1.19 [0.60, 2.37] ( <i>P</i> =0.62)	
Diabetes mellitus			0.27
No	106	0.56 [0.19, 1.66] ( <i>P</i> =0.29)	
Yes	185	1.11 [0.56, 2.20] ( <i>P</i> =0.76)	
Renal function			0.59
eGFR ≥ 30	165	1.07 [0.50, 2.26] ( <i>P</i> =0.87)	
eGFR < 30	58	0.61 [0.17, 2.21] ( <i>P</i> =0.46)	
On dialysis	68	0.82 [0.26, 2.57] ( <i>P</i> =0.73)	
Coronary artery disease			0.15
No	123	0.50 [0.17, 1.45] ( <i>P</i> =0.20)	
Yes	168	1.22 [0.60, 2.51] ( <i>P</i> =0.58)	
Cerebrovascular disease			0.11
No	210	1.20 [0.61, 2.35] ( <i>P</i> =0.60)	
Yes	81	0.48 [0.17, 1.32] ( <i>P</i> =0.15)	
Aspirin use			0.81
No	30	0.70 [0.08, 5.83] ( <i>P</i> =0.74)	
Yes	261	0.91 [0.50, 1.68] ( <i>P</i> =0.77)	
Thienopyridine use			0.35
No	73	0.48 [0.11, 2.17] ( <i>P</i> =0.34)	
Yes	218	1.01 [0.54, 1.91] ( <i>P</i> =0.96)	

(Cont. Table 4)

	<i>n</i>	Hazard ratio [95% confidence interval] of TLR vs. Observation for arterial occlusion	<i>P</i> for interaction
Cilostazol use			0.56
No	208	0.97 [0.51, 1.85] (P=0.93)	
Yes	83	0.68 [0.22, 2.12] (P=0.50)	
Rutherford classification			0.008
Category 0	79	5.44 [1.42, 20.9] (P=0.014)	
Category 1	94	1.18 [0.42, 3.32] (P=0.75)	
Category 2	118	0.59 [0.29, 1.20] (P=0.14)	
ABI			0.22
< 0.68	105	1.08 [0.56, 2.07] (P=0.83)	
≥ 0.68	184	0.50 [0.16, 1.53] (P=0.22)	
Restenotic pattern			0.52
Type I	119	1.16 [0.31, 4.40] (P=0.83)	
Type II	66	0.54 [0.11, 2.61] (P=0.44)	
Type III	39	0.98 [0.23, 4.18] (P=0.98)	
Type IV	31	1.33 [0.33, 5.42] (P=0.69)	
Type V	36	0.98 [0.41, 2.32] (P=0.96)	
Aortoiliac revascularization			0.56
No	179	1.02 [0.50, 2.08] (P=0.96)	
Yes	112	0.73 [0.29, 1.85] (P=0.51)	
TASC II classification			0.18
Class A/B	128	1.35 [0.52, 3.47] (P=0.54)	
Class C/D	163	0.65 [0.32, 1.30] (P=0.22)	
Chronic total occlusion			0.80
No	138	0.91 [0.35, 2.37] (P=0.84)	
Yes	153	0.78 [0.38, 1.62] (P=0.51)	
PACSS classification			0.69
Grade 0	78	1.21 [0.46, 3.21] (P=0.70)	
Grade 1	59	0.32 [0.07, 1.54] (P=0.16)	
Grade 2	70	0.94 [0.33, 2.62] (P=0.90)	
Grade 3	30	1.24 [0.23, 6.62] (P=0.80)	
Grade 4	54	1.09 [0.38, 3.13] (P=0.87)	
Stent use at initial EVT			0.58
None	63	1.23 [0.36, 4.18] (P=0.73)	
Spot stenting	48	0.82 [0.28, 2.42] (P=0.72)	
Full coverage	180	0.82 [0.40, 1.70] (P=0.60)	
Infrapopliteal runoff			0.064
0/1 runoff	111	1.63 [0.70, 3.84] (P=0.26)	
2/3 runoffs	177	0.62 [0.30, 1.30] (P=0.20)	

rence was determined solely based on reports from the patients, and no data on objective assessment of ischemia, exercise tolerance test, and other variables were available.

It cannot be ruled out that these aspects might have affected the results of the current study.

### Conclusions

Even if restenosis is detected during follow-up

after EVT for SFA, early intervention has been determined to not contribute to the improvement of clinical course in patients without recurred symptoms at the time of restenosis detection.

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