The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2020; 27: 769-779. http://doi.org/10.5551/jat.52647

Clinical Outcome and Diverse Risk Factors for Different Therapeutic Target Locations of Peripheral Artery Disease

Toshiyuki Ko[1], Michiaki Higashitani[2], Yukari Uemura[3], Makoto Utsunomiya[4], Tetsuo Yamaguchi[5], Akihiro Matsui[6], Shunsuke Ozaki[7], Kazuki Tobita[8], Takahide Kodama[5], Hiroyuki Morita[1] and Issei Komuro[1]

[1]Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[2]Department of Cardiology, Tokyo Medical University Ibaraki Medical Center, Ibaraki, Japan
[3]Biostatistics Section, Department of Data Science, Center of Clinical Science, National Center for Global Health and Medicine, Tokyo, Japan
[4]Department of Cardiology, Toho University Ohashi Medical Center, Tokyo, Japan
[5]Department of Cardiology, Toranomon Hospital, Tokyo, Japan
[6]Department of Cardiology, Kasukabe Chuo General Hospital, Saitama, Japan
[7]Department of Cardiology, Itabashi Chuo Medical Center, Tokyo, Japan
[8]Department of Cardiovascular Medicine, Shonan Kamakura General Hospital, Kanagawa, Japan

Aim: Previous studies on peripheral artery disease (PAD) only enrolled patients with atherosclerotic lesion limited to any one of isolated locations (aortoiliac [AI], femoropopliteal [FP], and below the knee [BTK]). However, the interventions for PAD in a real-world clinical setting are often simultaneously performed for several different locations.

Methods: We conducted a prospective multicenter study that included 2,230 patients with PAD who received intervention for lower extremity lesions in each area and across different areas. Patients were divided into 7 groups according to the combination of treatment locations. Overall survival (OS), major adverse limb events (MALEs), and risk factors for OS and MALEs were statistically analyzed.

Results: After adjustment for confounding factors, the attributable risk for OS was similar among isolated AI, FP, and BTK treatments. MALEs increased in correlation with the number of treatment locations. Dialysis and critical limb ischemia were the common risk factors for OS and MALEs. However, the contribution of other factors such as type of drug usage was different according to treatment locations.

Conclusions: In patients with PAD, OS was largely defined by comorbidities but not by lesion location. The background risk factors, underlying comorbidities, and event rates were different according to PAD location, suggesting that stratified treatment should be established for different patient populations.

Key words: Endovascular therapy, Peripheral artery disease, Target location, Real-world data

Introduction

Peripheral artery disease (PAD) is a systemic atherothrombotic disease in which plaque builds up in the arteries that supply blood to the limbs. Approximately 200 million individuals worldwide are estimated to experience lower extremity PAD[1]. Despite remarkable advances in both medication and intervention therapies, the global prevalence of PAD continues to increase, and patients with PAD are at a high risk for developing major adverse cardiovascular events and major adverse limb events (MALEs)[2, 3]. To date, several previous studies have reported the prognosis and therapeutic outcomes of PAD[4-6]. Prior studies on endovascular therapy (EVT) examined target lesions limited to any one of isolated locations (aortoiliac [AI], femoropopliteal [FP], and below the knee [BTK]); however, the interventions for PAD in a real-

Address for correspondence: Michiaki Higashitani, Department of Cardiology, Tokyo Medical University Ibaraki Medical Center, 3-20-1 Amicho-Chuo, Inashiki, Ibaraki 300-0395, Japan E-mail: mhigashi@tokyo-med.ac.jp

Received: August 26, 2019 Accepted for publication: October 20, 2019

world clinical setting are often simultaneously performed for several different locations. In addition, no previous prospective study on EVT has included all indications (claudication, critical limb ischemia, and acute limb ischemia) for patients with PAD. Therefore, a prospective multicenter study that covers all locations and indications is required to reveal real-world data.

Our group has recently reported the Toma-Code (TOkyo taMA peripheral vascular intervention research COmraDE study) registry[7]. This registry is unique in that it prospectively enrolled all patients with PAD at each lower limb location and did not exclude patients with multiple lesions. Moreover, this registry included all indications (claudication, critical limb ischemia, and acute limb ischemia).

Aim

The present study aimed to clarify patient characteristics and prognosis according to different treatment locations; to evaluate difference in the prognostic impact of treatment locations and their combinations using real-world data from the Toma-Code registry; and to clarify difference in risk factors for each treatment location.

Methods

Study Population and Design

The Toma-Code registry is a multicenter prospective registry that included 2230 consecutive patients with lower extremity PAD who underwent EVT in Japan from August 2014 to August 2016. All therapeutic indications were judged based on 2016 AHA/ACC Guideline on PAD[7]. A total of 6 university hospitals, 23 general hospitals, and 5 cardiovascular specialty hospitals participated in this study. The number of EVT procedures performed at these 34 hospitals per year was as follows: 2 facilities, 1–20; 7 facilities, 21–50; 11 facilities, 51–100; 7 facilities, 101–150; 3 facilities, 151–200; 2 facilities, 201–300; and 2 facilities, ≥ 301. The follow-up rate was 97.4% (prognostic data of 2,173 patients were analyzed), and the median follow-up period was 10.4 months.

In the present study, the participants were divided into the following 7 groups according to the combination of treatment locations: AI, FP, BTK, AI + FP, FP + BTK, AI + BTK, and AI + FP + BTK. Additionally, we studied the prognosis of each group. For example, if a patient received EVT in the AI and FP areas, then the patient would be assigned to the AI+FP group.

Clinical Measurements and Outcomes

Clinical measurement methods in the Toma-Code registry have been previously published[8]. Briefly, demographic, laboratory, and procedural data were collected from each patient's hospital chart or from database by independent researchers according to predetermined definitions, and the independent study office collectively managed all data. Patients were followed up at 1, 6, 12, 18, and 24 months after EVT. The major endpoints were all-cause death (overall survival [OS]) and MALEs, which were recorded from each institution's electronic health record system. A telephone survey of patients who were not followed up at each hospital after EVT was conducted to obtain recent information. MALE was defined as unscheduled major amputation, unscheduled major lower limb surgery or endovascular treatment, and acute limb ischemia event that required hospitalization. Furthermore, acute limb ischemia event was defined as limb-threatening ischemia that was confirmed using limb hemodynamic parameters or imaging and that led to the provision of an acute vascular intervention within 14 days of symptom onset[9]. Critical limb ischemia was defined as chronic ischemic pain at rest, ulcers, or gangrene, resulting in hospitalization and intervention[7]. Major amputation was defined as amputation due to a vascular event above the forefoot.

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Sakakibara Heart Institute (reference no. 14-023) and the committees of each participating facility. All patients provided written informed consent for their participation in the study. This study was registered at the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR no. UMIN000015100).

Statistical Analysis

Baseline parameters of each treatment location group are expressed as mean with standard deviation for continuous variables and as frequencies and proportions (percentages) for categorical variables. Difference among treatment location groups was assessed using analysis of variance and Fisher's exact test for continuous and categorical variables, respectively. Kaplan–Meier (KM) methods and log-rank test were employed to assess the effect of each treatment location group on the endpoints (OS, MALEs). Hazard ratios of each variable for endpoints (OS, MALEs) were calculated using Cox multivariate analysis after adjustment for potential confounding factors such as comorbidities and type of drug usage. All analyses were performed using SAS software package version 9.4 (SAS Institute, Cary, NC, USA). A probability

value of $p<0.05$ for all tests was considered statistically significant.

Results

Study Population Characteristics

A total of 2230 patients were enrolled within the study period and were distributed as follows to each combination of treatment locations: AI, 461 patients; FP, 850 patients; BTK, 230 patients; AI + FP, 314 patients; FP + BTK, 321 patients; AI + BTK, 10 patients; and AI + FP + BTK, 44 patients. **Fig. 1** shows the distribution of patients in this study. Only 10 procedures were performed in the AI + BTK group, which were difficult to statistically analyze; hence, we did not include this group in the subsequent analysis.

Clinical characteristics and laboratory data before EVT are summarized in **Table 1**. The patients in this study were predominantly males (71.5%). Patients who received EVT at locations that involved the BTK area (BTK, AI + BTK, FP + BTK) tended to have a low body mass index (<18), severe diabetes mellitus (DM) requiring insulin treatment, dialysis complication, heart failure, coronary artery disease, cerebrovascular disease, and history of major amputation. Furthermore, they tended to receive EVT more for critical limb ischemia than for claudication as treatment indication.

Outcomes

Fig. 2 and **Table 2** show the KM curves and Cox multivariate analysis for patients who received EVT at each combination of target locations (AI, FP, BTK, AI + FP, FP + BTK, AI + FP + BTK). Moreover, we analyzed and compared the hazard ratios for all combination patterns of treatment locations (**Supplementary Fig. 1**). Raw KM curves for OS and MALEs are shown in **Fig. 2a and 2b**, whereas KM curves after adjustment for each clinical factor (adjusted KM curves) are presented in **Fig. 2c and 2d**. KM curves showed that both OS and MALEs were significantly worse in patients receiving treatment that involved the BTK area than in those who only received treatment without involvement of BTK areas (**Fig. 2a and 2b**). Adjusted KM curves represent the essential prognostic impact of PAD at each location. For instance, although the isolated BTK treatment group had poorer prognosis than the isolated AI as well as isolated FP groups (**Fig. 2a**), the essential prognostic impact of PAD in the isolated BTK area itself is equal to that in the isolated AI as well as isolated FP areas (**Fig. 2c**). MALEs continuously occurred during the follow-up period after EVT in the isolated FP area, whereas the KM curves for treatment involving both the AI and BTK areas reached a plateau after 1–1.5 years passed. **Supplementary Table 1-3** show the Cox multivariate analysis for PAD in the isolated AI, AI + FP, and AI + FP + BTK areas; isolated FP, AI + FP, FP + BTK, and AI + FP + BTK areas; and isolated BTK, FP + BTK, and AI + FP + BTK areas, respectively. These Cox multivariate analysis for each classified group showed that both benign and adverse prognostic factors were different according to each PAD location. With respect to OS, critical limb ischemia, left ventricular ejection fraction <50%, and dialysis were common negative risk factors among all PAD locations. Major negative risk factors associated with MALEs were dialysis and critical limb ischemia. However, several differences in prognostic factors were also observed among treatment groups classified according to target locations (**Supplementary Table 1-3**). **Table 3** presents the event rates per 100 person-years for OS and MALEs according to procedures performed at each treatment location. Treatment in the FP and BTK areas resulted in 20–30% and >50% MALEs/year, respectively. Finally, **Table 4** shows the details of death events and MALE according to the target area in EVT. There was no significant differences in the causes of events among six groups.

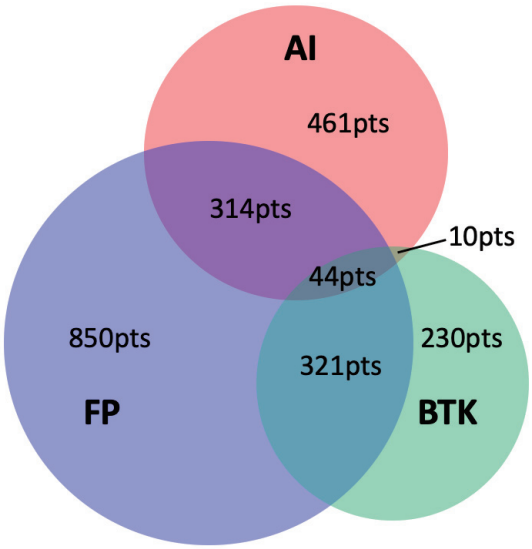


Fig. 1. Numbers of interventional procedures performed at each different disease location

Venn diagram of procedure counts for each different disease location and their combinations. AI, aortoiliac; BTK, below the knee; FP, femoropopliteal; pts, patients.

Discussion

Several previous studies have indicated an unfavorable prognosis for PAD in Japan and Western

Table 1. Baseline patient characteristics of each EVT group

	AI (n = 461)	FP (n = 850)	BTK (n = 230)	AI + FP (n = 314)	FP + BTK (n = 321)	AI + FP + BTK (n = 44)	AI + BTK (n = 10)	p-value
Age, mean ± SD (years)	72.6 ± 8.4	73.2 ± 9.3	71.4 ± 11.5	74.1 ± 8.5	74.7 ± 9.4	74.3 ± 8.2	76.6 ± 10.3	0.001
Male gender, n (%)	376 (81.6%)	574 (67.5%)	167 (72.6%)	238 (75.8%)	200 (62.3%)	33 (75.0%)	7 (70%)	< 0.0001
BMI, mean ± SD (kg/m^2)	22.7 ± 3.0	22.8 ± 3.6	22.4 ± 3.9	22.1 ± 3.9	21.7 ± 3.9	21.1 ± 3.3	18.7 ± 3.0	< 0.0001
BMI < 18, n (%)	16 (3.5%)	55 (6.5%)	28 (12.5%)	37 (11.9%)	45 (14.2%)	8 (18.2%)	4 (40.0%)	< 0.0001
ABI (Rt), mean ± SD	0.82 ± 0.23	0.78 ± 0.21	0.91 ± 0.24	0.70 ± 0.20	0.77 ± 0.23	0.67 ± 0.21	0.92 ± 0.16	< 0.0001
ABI (Lt), mean ± SD	0.78 ± 0.22	0.78 ± 0.21	0.89 ± 0.24	0.66 ± 0.19	0.78 ± 0.22	0.69 ± 0.24	0.95 ± 0.24	< 0.0001
SBP, mean ± SD (mmHg)	136.7 ± 21.4	138.2 ± 23.0	135.82 ± 34.5	138.3 ± 23.4	139.1 ± 24.7	148.7 ± 29.0	137.7 ± 24.7	0.038
DBP, mean ± SD (mmHg)	74.2 ± 14.5	74.1 ± 13.9	74.17 ± 15.1	72.6 ± 12.9	72.9 ± 14.6	78.2 ± 14.6	74.4 ± 16.3	0.220
HR, mean ± SD (bpm)	73.5 ± 13.7	74.7 ± 13.7	80.74 ± 14.8	75.5 ± 16.1	77.3 ± 16.7	75.1 ± 16.9	74.5 ± 15.3	< 0.0001
DM (diet therapy), n (%)	40 (8.7%)	81 (9.5%)	28 (12.2%)	38 (12.1%)	31 (9.7%)	5 (11.4%)	3 (30.0%)	< 0.0001
DM (oral drug), n (%)	100 (21.7%)	250 (29.4%)	61 (26.5%)	81 (25.8%)	105 (32.7%)	13 (29.5%)	1 (10.0%)	
DM (insulin), n (%)	54 (11.7%)	171 (20.1%)	64 (27.8%)	44 (14.0%)	82 (25.5%)	11 (25.0%)	2 (20.0%)	
Past smoker, n (%)	184 (39.9%)	303 (35.6%)	82 (35.7%)	108 (34.4%)	97 (30.2%)	15 (34.1%)	5 (50.0%)	< 0.0001
Current smoker, n (%)	121 (26.3%)	209 (24.6%)	36 (15.7%)	91 (29.0%)	36 (11.2%)	9 (20.5%)	3 (30.0%)	
HTN, n (%)	378 (82.0%)	735 (86.5%)	166 (72.2%)	266 (84.7%)	249 (77.6%)	38 (86.4%)	7 (70.0%)	< 0.0001
DL, n (%)	299 (64.9%)	526 (61.9%)	104 (45.2%)	186 (59.2%)	132 (41.1%)	23 (52.3%)	2 (20.0%)	< 0.0001
Dialysis, n (%)	45 (9.8%)	182 (21.4%)	148 (64.3%)	62 (19.7%)	153 (47.7%)	16 (36.4%)	3 (30.0%)	< 0.0001
Heart failure, n (%)	37 (8.0%)	97 (11.4%)	42 (18.3%)	35 (11.1%)	53 (16.5%)	10 (22.7%)	0 (0%)	< 0.0001
LVEF < 50%, n (%)	34 (7.4%)	81 (9.5%)	43 (18.7%)	33 (10.5%)	43 (13.4%)	3 (6.8%)	2 (20.0%)	< 0.0001
CAD, n (%)	202 (43.8%)	405 (47.6%)	120 (52.2%)	140 (44.6%)	166 (51.7%)	22 (50.0%)	3 (30.0%)	0.160
CVD, n (%)	51 (11.1%)	121 (14.2%)	38 (16.5%)	47 (15.0%)	55 (17.1%)	11 (25.0%)	0 (0%)	0.047
AF, n (%)	38 (8.2%)	75 (8.8%)	34 (14.8%)	35 (11.1%)	54 (16.8%)	6 (13.6%)	1 (10.0%)	< 0.0001
Non-ambulatory status, n (%)	14 (3.0%)	54 (6.4%)	38 (16.5%)	25 (8.0%)	80 (24.9%)	13 (29.5%)	2 (20.0%)	< 0.0001
AS, n (%)	7 (1.5%)	10 (1.2%)	9 (3.9%)	7 (2.2%)	16 (5.0%)	0 (0%)	0 (0%)	0.008
Hx of major amputation, n (%)	4 (0.9%)	18 (2.1%)	17 (7.4%)	4 (1.3%)	24 (7.5%)	4 (9.1%)	0 (0%)	< 0.0001
Hx of lower extremity bypass, n (%)	11 (2.4%)	34 (4.0%)	11 (2.4%)	12 (3.8%)	11 (3.4%)	4 (9.1%)	2 (20.0%)	0.220
Hx of PVI to the lower extremity, n (%)	53 (11.5%)	223 (26.3%)	74 (32.2%)	56 (17.9%)	78 (24.3%)	11 (25%)	2 (20.0%)	< 0.0001
ALI, n (%)	14 (3.0%)	28 (3.4%)	10 (4.3%)	8 (2.5%)	19 (5.9%)	4 (9.1%)	1 (10.0%)	< 0.0001
Claudication, n (%)	397 (86.1%)	675 (79.6%)	15 (6.6%)	240 (76.4%)	61 (19.0%)	7 (15.9%)	0 (0%)	
CLI, n (%)	50 (10.9%)	144 (17.0%)	205 (89.1%)	66 (21.1%)	240 (74.8%)	33 (75.0%)	9 (90.0%)	
ACEI/ARB, n (%)	262 (56.8%)	519 (61.1%)	78 (33.9%)	175 (55.7%)	130 (40.5%)	21 (47.7%)	3 (30.0%)	< 0.0001
Aspirin, n (%)	338 (73.7%)	592 (69.6%)	146 (63.5%)	216 (68.8%)	211 (65.7%)	32 (72.7%)	5 (50.0%)	0.12
Thienopyridine, n (%)	346 (75.1%)	574 (67.5%)	125 (54.3%)	225 (71.7%)	199 (62.0%)	30 (68.2%)	7 (70.0%)	< 0.0001
Cilostazol, n (%)	139 (30.2%)	360 (42.4%)	81 (35.2%)	139 (44.3%)	120 (37.4%)	16 (36.4%)	4 (40.0%)	0.0004
Statin, n (%)	271 (58.8%)	484 (56.9%)	79 (34.3%)	165 (52.5%)	113 (35.2%)	17 (38.6%)	1 (10.0%)	< 0.0001

Values are presented as mean ± standard deviation or as number (%).
ABI, ankle–brachial index; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AF, atrial fibrillation; AI, aortoiliac; ALI, acute limb ischemia; AS, aortic stenosis; BMI, body mass index; BTK, below the knee; CAD, coronary artery disease; CLI, critical limb ischemia; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DL, dyslipidemia; DM, diabetes mellitus; EVT, endovascular therapy; FP, femoropopliteal; HR, heart rate; HTN, hypertension; Hx, history; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; SD, standard deviation.

countries[10-12]. Many registries for studying the etiology and prognosis of PAD were previously reported; nonetheless, all of these have narrowed their study population by limiting the indications and target locations in the lower limbs. In contrast, we provided the first multicenter prospective cohort registry that included all interventions irrespective of target locations and indications (e.g., not only patients with claudication or critical limb ischemia but also those with acute limb ischemia event were included). Thus, this registry revealed real-world data on EVT for PAD in current clinical practice.

Fig. 3 illustrates the association between risk factors and the level of each PAD location (isolated AI, FP, or BTK) based on the results presented in **Table 1**. The results of our study, which enrolled patients

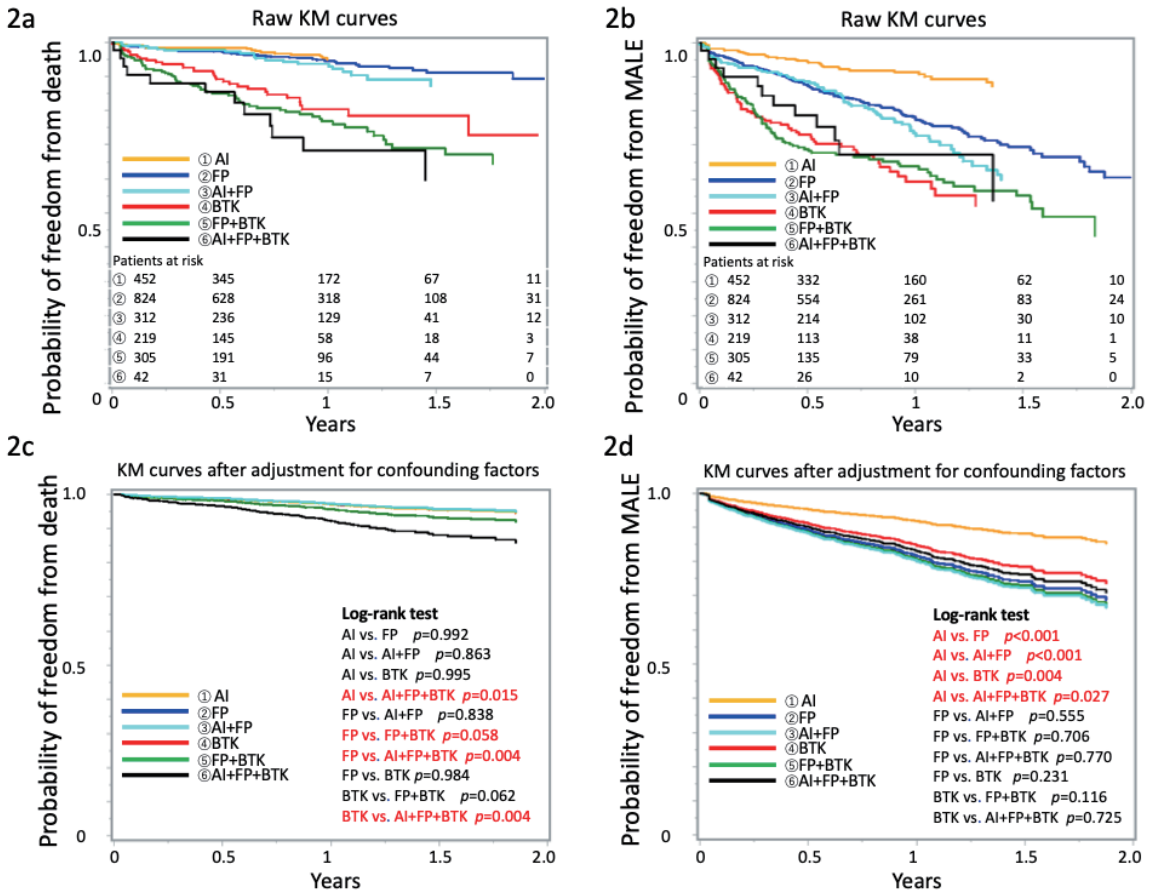


Fig. 2. Raw and adjusted KM curves for patients

a, b: Raw KM curves for OS and MALEs in patients. c, d: KM curves after adjustment for each underlying clinical factor. AI, aortoiliac; BTK, below the knee; FP, femoropopliteal; MALEs, major adverse limb events; OS, overall survival.

receiving EVT, are basically consistent with those of a previous study[13] in that the clinical phenotype of peripheral atherosclerosis varies with the prevalence of cardiovascular risk factors such as gender, DM, dyslipidemia, and smoking. In addition, we further investigated considerably more types of comorbidities in the present study. Compared with patients who received EVT at the isolated AI or FP level, patients who received EVT at the BTK level tended to have severe comorbidities (e.g., severe DM, end-stage renal disease requiring dialysis, heart failure) and other vascular diseases (e.g., coronary artery disease, cerebrovascular disease). Therefore, they are thought to be at the end stage of atherosclerotic diseases. Likewise, comorbidity of atrial fibrillation, which is one of the diseases related to atherosclerosis, was largely more prevalent in patients with BTK lesion than in those with AI or FP lesion. This result is in agreement with the finding of a previous study that reported a much higher prevalence of atrial fibrillation in PAD patients with severe disease status[14]. Uniquely, patients with FP lesion were predominantly females and tended to have hypertension compared with other patients, suggesting the pathogenesis of PAD at the FP level might be different from that of PAD at other levels.

Based on clinical experience, it could be comprehensible that patients with PAD in the BTK area have poor prognosis. In our registry, as shown in **Fig. 2a**, patients with isolated lesion in the BTK area and multiple lesions involving the BTK area had poor prognosis, as compared with those with lesions limited to other areas. However, only severe PAD with lesions distributed over all areas (AI + FP + BTK) showed a significant survival risk after adjustment for other confounding factors (**Fig. 2c**). This result is inconsistent with the finding of a previous retrospective cohort study, which showed that distal disease location was associated with worse survival after adjustment for potential confounders[15]. Our data suggest that OS was largely defined by patient background (including underlying diseases, comorbidities, and dialysis), but not by lesion location alone. Although we did not

Table 2. Multivariate Cox analysis for OS and MALEs

Risk factors for OS	HR (95% CI)	*p*-value	Risk factors for MALEs	HR (95% CI)	*p*-value
Age in 10-year increments	1.65 (1.31-2.07)	<0.0001	Age in 10-year increments	1.03 (0.91-1.17)	0.643
BMI <18	1.79 (0.96-3.34)	0.068	BMI <18	1.54 (1.01-2.35)	0.048
DM	1.56 (0.97-2.49)	0.066	DM	1.00 (0.77-1.30)	0.999
Dialysis	3.39 (2.06-5.60)	<0.0001	Dialysis	1.46 (1.09-1.97)	0.012
CVD	2.26 (1.34-3.66)	0.001	CVD	1.17 (0.83-1.64)	0.379
LVEF <50%	2.19 (1.29-3.72)	0.004	LVEF <50%	1.13 (0.78-1.66	0.515
ALI (vs. Claudication)	1.83 (0.59-5.70)	0.265	ALI (vs. Claudication)	1.63 (0.80-3.31)	0.178
CLI (vs. Claudication)	2.50 (1.42-4.42)	0.002	CLI (vs. Claudication)	2.76 (2.02-3.78)	<0.0001
ACEI/ARB	0.67 (0.43-1.05)	0.082	ACEI/ARB	0.79 (0.61-1.02)	0.070
Aspirin	0.65 (0.39-1.07)	0.089	Aspirin	0.79 (0.59-1.06)	0.116
Thienopyridine	0.51 (0.32-0.80)	0.004	Thienopyridine	0.96 (0.72-1.28)	0.782
Cilostazol	0.47 (0.28-0.78)	0.003	Cilostazol	0.82 (0.61-1.09)	0.173
Statin	0.79 (0.50-1.23)	0.294	Statin	1.09 (0.84-1.41)	0.518
FP (vs. AI)	1.00 (0.55-1.79)	0.992	FP (vs. AI)	2.36 (1.65-3.39)	<0.0001
BTK (vs. AI)	1.00 (0.52-1.94)	0.995	BTK (vs. AI)	1.93 (1.23-3.02)	0.004
AI + FP (vs. AI)	0.94 (0.47-1.88)	0.863	AI + FP (vs. AI)	2.57 (1.72-3.84)	<0.0001
FP + BTK (vs. AI)	1.51 (0.82-2.78)	0.891	FP + BTK (vs. AI)	2.49 (1.65-3.77)	<0.0001
AI + FP + BTK (vs. AI)	2.71 (1.21-6.05)	0.015	AI + FP + BTK (vs. AI)	2.16 (1.09-4.25)	0.027

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AI, aortoiliac; ALI, acute limb ischemia; BMI, body mass index; BTK, below the knee; CI, confidence interval; CLI, critical limb ischemia; CVD, cerebrovascular disease; DM, diabetes mellitus; FP, femoropopliteal; HR, hazard ratio; LVEF, left ventricular ejection fraction; MALEs, major adverse limb events; OS, overall survival.

Table 3. Event rates per 100 person-years of all-cause death and MALEs according to the target area in EVT

	Number of pts	All-cause death		MALEs	
		Events	n/100 pts-year	Events	n/100 pts-year
AI	461	16	4	37	9.6
FP	850	44	6	167	25.8
BTK	230	34	21.4	70	57.6
AI + FP	314	21	7.5	74	29.9
FP + BTK	321	65	27.3	104	55.2
AI + FP + BTK	44	12	34	12	44.4

AI, aortoiliac; BTK, below the knee; FP, femoropopliteal; MALEs, major adverse limb events; pts, patients; EVT, endovascular therapy.

investigate lower limb muscle strength and activities of daily living, patients with multiple and widespread PAD lesions from the AI area to the BTK area are considered to have considerably impaired muscle strength and activities of daily living, which may adversely affect the patient's prognosis[16, 17].

With respect to MALEs, the prognosis of treatment for the FP area was surprisingly even worse than that for the BTK area after adjustment for each underlying clinical factor. As the mortality rate was relatively high in patients with lesions involving the BTK area, some patients had probably died prior to experiencing adverse limb events. However, further investigations are required to elucidate this contradictory prognosis between FP and BTK lesions. MALE as an outcome in patients receiving EVT for the FP area was reported in 2010 [6], which is similar to our data. This indicates that the outcome of EVT for the FP area has not sufficiently improved despite technical advances in recent years.

Notably, other prognostic factors such as type of drug usage were different according to PAD location, suggesting that there might be different pathogenesis for each type of disease location. Aspirin use was an independent benign prognostic factor in patients who received EVT in the AI and FP areas. However, no significant effect of aspirin use on OS was observed in patients with BTK lesion. We assume that this is because the disease severity of PAD and other underlying comorbidities are much more serious in patients

Table 4. The details of Death events and MALE according to the target area in EVT

Death	Cardiac death	Non-cardiovascular death	*p*-value
AI	3	13	0.952
FP	15	29	
BTK	9	25	
AI + FP	8	13	
FP + BTK	18	47	
AI + FP + BTK	2	10	

MALE	Unscheduled major amptation	Unscheduled major lower limb surgery	Unscheduled endovascular treatment	Acute limb ischemia	*p*-value
AI	6	9	22	2	0.080
FP	18	13	138	6	
BTK	17	3	50	2	
AI + FP	2	2	64	4	
FP + BTK	18	6	78	2	
AI + FP + BTK	1	0	11	1	

AI, aortoiliac; BTK, below the knee; FP, femoropopliteal; MALEs, major adverse limb events; pts, patients; EVT, endovascular therapy.

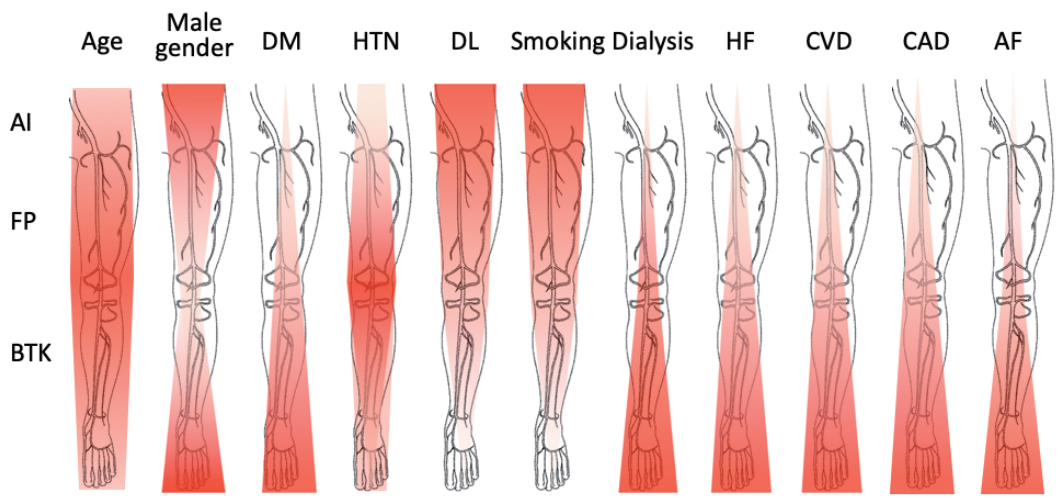


Fig. 3. Association between risk factors and each level of atherosclerotic target lesions

Red overlay on the anatomic cartoon illustrates the incidence of each type of risk factors associated with the pattern of atherosclerotic lesions. The darker red color denotes the location in which comorbidities were mostly observed in the study population. AF, atrial fibrillation; AI, aortoiliac; BTK, below the knee; CAD, coronary artery disease; CVD, cerebrovascular disease; DL, dyslipidemia; DM, diabetes mellitus; FP, femoropopliteal; HF, heart failure; HTN, hypertension.

with vascular stenosis in the BTK area; thus, aspirin use is no longer effective. With respect to cilostazol use, our result was consistent with that of previous reports that described the benefit of cilostazol for reducing MALEs[18, 19]. Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use was an independent benign prognostic factor in patients who received EVT in the AI and BTK areas. This result is consistent with that of previous studies that reported angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use to be beneficial for patients at high risk for cardiovascular events[20, 21].

Interestingly, the beneficial effect of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use on OS could not reach statistical significance in patients with FP lesion; however, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use showed significantly benign effect on MALEs in those with FP lesion. Although we cannot find reasonable explanation for this result at this

point, the background pathogenesis of FP lesion might be considerably different from that of AI or BTK lesions. As for statin, previous reports from the sub-analysis of a large cohort registry showed that statin use was associated with a 20–25% risk reduction in major adverse cardiovascular events and ~18% risk reduction in adverse limb outcomes (including worsening symptoms, peripheral revascularization, and ischemic amputations)[22, 23]. However, in our study, statin use could not reach statistical significance for better OS and MALE outcomes. All patients enrolled in our study received EVT for PAD; conversely, previous studies to study the impact of statin use for PAD[22, 23] enrolled only patients diagnosed with symptomatic PAD. Taking this into account, statin use is probably beneficial only for patients in the relatively early stage of PAD. This postulation can be supported by our present findings in which the beneficial effect on MALEs showed marginal significance in patients who received EVT for AI lesion (which was thought to be relatively mild with respect to disease severity) (**Supplementary Table 1**).

In our study, the event rate of all-cause death adjusted for potential confounding factors was high only in the case of disease location involving the BTK area. However, only disease location limited to the AI lesion showed a low rate of MALEs. Even procedures involving the FP and AI + FP lesions had a high event rate of 25.8 and 29.9 per 100 person-years, respectively. Despite advances in EVT for PAD, our data indicate that patency after EVT is permissible only in the treatment for AI lesion.

Study Limitations

Our registry included a large number of participants with PAD from several institutions and provided the latest real-world evidence; nevertheless, the present study has several limitations. First, our study only included Japanese patients; thus, whether its results can be directly applied to patients of other ethnicities remains unclear. Second, although all patients enrolled in our registry were considered for the indication of EVT according to the latest American Heart Association/American College of Cardiology guidelines[7], there might be some differences in treatment indication among hospitals. Finally, the follow-up period of our registry was relatively short. Therefore, we will perform long-term follow-up of this study population.

Conclusions

The present study showed real-world evidence on percutaneous intervention for lower extremity PAD according to disease locations including multiple lesions. The background risk factors, underlying comorbidities, and event rates were different according to PAD location, suggesting that stratified treatment should be established for different patient populations. Despite various advances in medication and interventional technology for PAD in recent years, the outcomes remain unsatisfactory. Further innovation of treatment techniques and improvement in treatment strategy are warranted.

Acknowledgements

The authors thank the Office of Administrative and Accounting Support for Clinical Research of Sakakibara Heart Institute, especially Mrs. Yoshiko Shimomura. The Toma-Code Registry would have been unsuccessful without her assistance.

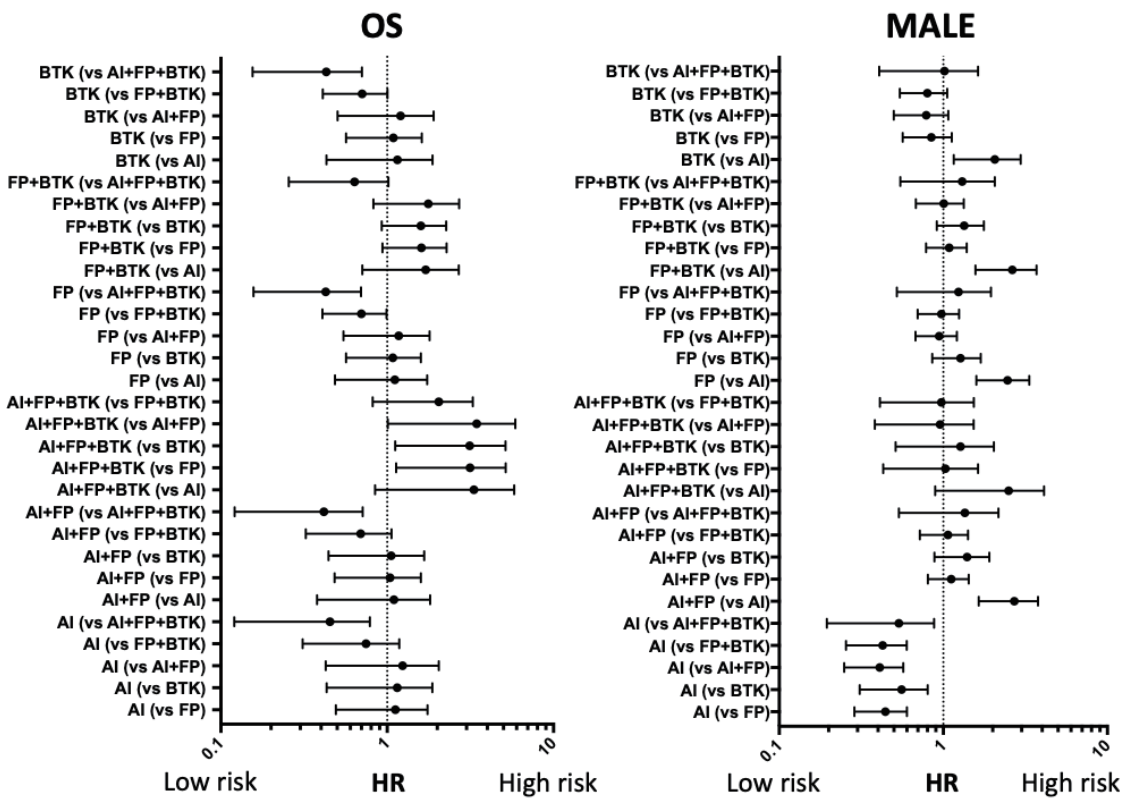
Disclosures

This work was supported by the Vascular Disease Research Project of the Japan Research Promotion Society for Cardiovascular Diseases. All authors have no relationship with the industry and other relevant entities to disclose.

References

1) Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet, 2013; 382: 1329-1340
2) Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res, 2015; 116: 1509-1526
3) Hess CN, Norgren L, Ansel GM, Capell WH, Fletcher JP, Fowkes FGR, Gottsäter A, Hitos K, Jaff MR, Nordanstig J, Hiatt WR. A structured review of antithrombotic therapy in peripheral artery disease with a focus on revascularization: a TASC (InterSociety Consensus for the Management of Peripheral Artery Disease) initiative. Circulation, 2017; 135: 2534-2555
4) Tsujimura T, Iida O, Fujita M, Masuda M, Okamoto S, Ishihara T, Nanto K, Kanda T, Okuno S, Matsuda Y, Fujihara M, Yokoi Y, Mano T. Two-year Clinical Outcomes Post Implantation of EpicTM Self-Expanding Nitinol Stents for the Aortoiliac Occlusive Disease in Patients with Peripheral Arterial Disease. J Atheroscler Thromb, 2018; 25: 344-349
5) Giles KA, Pomposelli FB, Spence TL, Hamdan AD, Blattman SB, Panossian H, Schermerhorn ML. Infrapopliteal angioplasty for critical limb ischemia: relation of TransAtlantic InterSociety Consensus class to outcome in 176 limbs. J Vasc Surg, 2008; 48: 128-136
6) Soga Y, Iida O, Hirano K, Yokoi H, Nanto S, Nobuyoshi

M. Mid-term clinical outcome and predictors of vessel patency after femoropopliteal stenting with self-expandable nitinol stent. J Vasc Surg, 2010; 52: 608-615
7) Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RA, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 2017; 135: e686-e725
8) Higashitani M, Uemura Y, Mizuno A, Utsunomiya M, Yamaguchi T, Matsui A, Ozaki S, Tobita K, Tosaka A, Oida A, Suzuki K, Kodama T, Jujo K, Doijiri T, Takahashi Y, Matsuno S, Kaneko N, Moriguchi A, Kishi S, Anzai H; Toma-Code Registry Investigators. Cardiovascular outcome and mortality in patients undergoing endovascular treatment for symptomatic peripheral artery disease - short-term results of the Toma-Code registry. Circ J, 2018; 82: 1917-1925
9) Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. N Engl J Med, 2012; 366: 2198-2206
10) Reinecke H, Unrath M, Freisinger E, Bunzemeier H, Meyborg M, Lüders F, Gebauer K, Roeder N, Berger K, Malyar NM. Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence. Eur Heart J, 2015; 36: 932-938
11) Diehm C, Allenberg JR, Pittrow D, Mahn M, Tepohl G, Haberl RL, Darius H, Burghaus I, Trampisch HJ; German Epidemiological Trial on Ankle Brachial Index Study Group. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. Circulation, 2009; 120: 2053-2061
12) Kumakura H, Kanai H, Aizaki M, Mitsui K, Araki Y, Kasama S, Iwasaki T, Ichikawa S. The influence of the obesity paradox and chronic kidney disease on long-term survival in a Japanese cohort with peripheral arterial disease. J Vasc Surg, 2010; 52: 110-117
13) Diehm N, Shang A, Silvestro A, Do DD, Dick F, Schmidli J, Mahler F, Baumgartner I. Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. Eur J Vasc Endovasc Surg, 2006; 31: 59-63
14) Conway DS, Lip GY. Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). Am J Cardiol, 2004; 93: 1422-1425
15) Chen Q, Smith CY, Bailey KR, Wennberg PW, Kullo IJ. Disease location is associated with survival in patients with peripheral arterial disease. J Am Heart Assoc, 2013; 2: e000304
16) Addison O, Prior SJ, Kundi R, Serra MC, Katzel LI, Gardner AW, Ryan AS. Sarcopenia in peripheral arterial disease: prevalence and effect on functional status. Arch Phys Med Rehabil, 2018; 99: 623-628
17) Sugai T, Watanabe T, Otaki Y, Goto J, Watanabe K, Toshima T, Takahashi T, Yokoyama M, Tamura H, Nishiyama S, Arimoto T, Takahashi H, Shishido T, Watanabe M. Decreased psoas muscle computed tomography value predicts poor outcome in peripheral artery disease. Circ J, 2018; 82: 3069-3075
18) Soga Y, Iida O, Hirano K, Suzuki K, Kawasaki D, Miyashita Y, Tsuchiya T, Nobuyoshi M. Impact of cilostazol after endovascular treatment for infrainguinal disease in patients with critical limb ischemia. J Vasc Surg, 2011; 54: 1659-1667
19) Soga Y, Yokoi H, Kawasaki T, Nakashima H, Tsurugida M, Hikichi Y, Nobuyoshi M. Efficacy of cilostazol after endovascular therapy for femoropopliteal artery disease in patients with intermittent claudication. J Am Coll Cardiol, 2009; 53: 48-53
20) Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med, 2000; 342: 145-153
21) ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med, 2008; 358: 1547-1559
22) Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg, 2007; 45: 645-654
23) Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Goto S, Ohman EM, Elbez Y, Sritara P, Baumgartner I, Banerjee S, Creager MA, Bhatt DL; REACH Registry Investigators. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. Eur Heart J, 2014; 35: 2864-2872



Supplementary Fig. 1. HR comparison of all combination patterns of treatment locations

AI, aortoiliac; BTK, below the knee; FP, femoropopliteal; HR, hazard ratio; MALE, major adverse limb events; OS, overall survival.

Supplementary Table 1. Multivariate Cox analysis for OS and MALEs in patients who received PVI in the AI, AI + FP, and AI + FP + BTK areas

Risk factors for OS	HR (95% CI)	*p*-value	Risk factors for MALEs	HR (95% CI)	*p*-value
Age in 10-year increments	1.26 (0.86-1.83)	0.234	Age in 10-year increments	0.88 (0.71-1.09)	0.235
BMI < 18	1.55 (0.67-3.57)	0.303	BMI < 18	2.09 (1.25-3.47)	0.005
DM	0.88 (0.46-1.66)	0.686	DM	1.18 (0.8-1.73)	0.407
Dialysis	2.95 (1.53-5.71)	0.001	Dialysis	1.72 (1.12-2.64)	0.013
CVD	0.95 (0.42-2.12)	0.894	CVD	1.29 (0.80-2.10)	0.299
LVEF < 50%	3.56 (1.71-7.38)	0.001	LVEF < 50%	1.19 (0.65-2.19)	0.569
ALI	3.52 (0.77-6.07)	0.105	ALI	2.35 (0.84-6.55)	0.102
CLI	4.71 (2.26-9.83)	< 0.0001	CLI	2.25 (1.46-3.47)	0.0002
ACEI/ARB	0.48 (0.25-0.94)	0.031	ACEI/ARB	1.03 (0.71-1.49)	0.876
Aspirin	0.48 (0.25-0.92)	0.026	Aspirin	0.83 (0.54-1.29)	0.410
Thienopyridine	0.66 (0.34-1.30)	0.232	Thienopyridine	0.95 (0.61-1.50)	0.835
Cilostazol	0.62 (0.32-1.20)	0.153	Cilostazol	0.59 (0.38-0.93)	0.022
Statin	1.12 (0.59-2.12)	0.731	Statin	0.71 (0.49-1.02)	0.065
AI + FP (vs. AI)	1.07 (0.52-2.23)	0.856	AI + FP (vs. AI)	2.53 (1.66-3.85)	< 0.0001
AI + FP + BTK (vs. AI)	2.99 (1.20-7.42)	0.018	AI + FP + BTK (vs. AI)	1.85 (0.89-3.86)	0.100

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AI, aortoiliac; ALI, acute limb ischemia; BMI, body mass index; BTK, below the knee; CI, confidence interval; CLI, critical limb ischemia; CVD, cerebrovascular disease; DM, diabetes mellitus; FP, femoropopliteal; HR, hazard ratio; LVEF, left ventricular ejection fraction; MALEs, major adverse limb events; OS, overall survival; PVI, percutaneous vascular intervention.

Supplementary Table 2. Multivariate Cox analysis for OS and MALEs in patients who received PVI in the FP, AI + FP, FP + BTK, and AI + FP + BTK areas

Risk factors for OS	HR (95% CI)	*p*-value	Risk factors for MALEs	HR (95% CI)	*p*-value
Age in 10-year increments	1.58 (1.28-1.94)	<0.0001	Age in 10-year increments	1.01 (0.9-1.12)	0.925
BMI <18	1.67 (1.06-2.65)	0.028	BMI <18	1.30 (0.93-1.82)	0.123
DM	1.67 (1.11-2.52)	0.014	DM	1.04 (0.83-1.31)	0.731
Dialysis	2.59 (1.76-3.82)	<0.0001	Dialysis	1.56 (1.22-1.99)	0.0004
CVD	1.42 (0.94-2.17)	0.10	CVD	1.08 (0.81-1.43)	0.620
LVEF <50%	3.18 (2.11-4.81)	<0.0001	LVEF <50%	1.26 (0.91-1.76)	0.167
ALI	3.48 (1.49-8.14)	0.004	ALI	1.72 (0.96-3.07)	0.068
CLI	3.08 (1.90-5.00)	<0.0001	CLI	2.04 (1.56-2.66)	<0.0001
ACEI/ARB	0.75 (0.52-1.08)	0.123	ACEI/ARB	0.73 (0.59-0.91)	0.005
Aspirin	0.65 (0.44-0.97)	0.034	Aspirin	0.81 (0.63-1.05)	0.110
Thienopyridine	0.80 (0.54-1.18)	0.250	Thienopyridine	0.98 (0.76-1.26)	0.850
Cilostazol	0.78 (0.52-1.17)	0.230	Cilostazol	0.85 (0.66-1.09)	0.197
Statin	0.90 (0.62-1.31)	0.590	Statin	1.04 (0.83-1.30)	0.726
AI + FP (vs. FP)	0.95 (0.55-1.66)	0.856	AI + FP (vs. FP)	1.09 (0.82-1.45)	0.543
FP + BTK (vs. FP)	1.55 (1.00-2.39)	0.049	FP + BTK (vs. FP)	1.12 (0.84-1.49)	0.442
AI + FP + BTK (vs. FP)	2.81 (1.41-5.58)	0.003	AI + FP + BTK (vs. FP)	1.00 (0.54-1.85)	0.997

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AI, aortoiliac; ALI, acute limb ischemia; BMI, body mass index; BTK, below the knee; CI, confidence interval; CLI, critical limb ischemia; CVD, cerebrovascular disease; DM, diabetes mellitus; FP, femoropopliteal; HR, hazard ratio; LVEF, left ventricular ejection fraction; MALEs, major adverse limb events; OS, overall survival; PVI, percutaneous vascular intervention.

Supplementary Table 3. Multivariate Cox analysis for OS and MALEs in patients who received PVI in the BTK, FP + BTK, and AI + FP + BTK areas

Risk factors for OS	HR (95% CI)	*p*-value	Risk factors for MALEs	HR (95% CI)	*p*-value
Age in 10-year increments	1.61 (1.28-2.02)	<0.0001	Age in 10-year increments	1.02 (0.88-1.19)	0.812
BMI <18	1.71 (1.07-2.75)	0.026	BMI <18	1.17 (0.75-1.81)	0.490
DM	1.46 (0.93-2.29)	0.103	DM	0.93 (0.66-1.31)	0.665
Dialysis	2.06 (1.31-3.22)	0.002	Dialysis	1.65 (1.18-2.30)	0.004
CVD	1.82 (1.13-2.91)	0.013	CVD	0.77 (0.5-1.20)	0.252
LVEF <50%	2.70 (1.69-4.32)	<0.0001	LVEF <50%	1.15 (0.75-1.77)	0.533
ALI	3.90 (1.23-12.36)	0.021	ALI	1.07 (0.40-2.84)	0.898
CLI	2.35 (1.00-5.51)	0.051	CLI	1.80 (1.08-2.98)	0.023
ACEI/ARB	0.45 (0.28-0.71)	0.001	ACEI/ARB	0.89 (0.64-1.22)	0.454
Aspirin	0.68 (0.44-1.07)	0.094	Aspirin	0.76 (0.54-1.09)	0.14
Thienopyridine	0.93 (0.60-1.46)	0.760	Thienopyridine	0.95 (0.67-1.34)	0.748
Cilostazol	0.75 (0.48-1.20)	0.230	Cilostazol	0.68 (0.47-0.99)	0.042
Statin	0.93 (0.59-1.46)	0.760	Statin	1.30 (0.94-1.79)	0.114
FP + BTK (vs. BTK)	1.45 (0.94-2.25)	0.093	FP + BTK (vs. BTK)	1.31 (0.94-1.82)	0.112
AI + FP + BTK (vs. BTK)	2.49 (1.24-5.01)	0.010	AI + FP + BTK (vs. BTK)	1.20 (0.63-2.28)	0.584

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AI, aortoiliac; ALI, acute limb ischemia; BMI, body mass index; BTK, below the knee; CI, confidence interval; CLI, critical limb ischemia; CVD, cerebrovascular disease; DM, diabetes mellitus; FP, femoropopliteal; HR, hazard ratio; LVEF, left ventricular ejection fraction; MALEs, major adverse limb events; OS, overall survival; PVI, percutaneous vascular intervention.