Cardiovascular Outcome and Mortality in Patients Undergoing Endovascular Treatment for Symptomatic Peripheral Artery Disease

— Short-Term Results of the Toma-Code Registry —

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Background: The present study was performed to clarify whether the preoperative clinical symptoms for endovascular therapy (EVT) can predict post-EVT death and cardiovascular prognosis in Japanese patients with peripheral artery disease (PAD), including acute disease.

Methods and Results: The TOKYO taMA peripheral vascular intervention research COMraDE (Toma-Code) Registry is a Japanese prospective cohort of 2,321 consecutive patients with PAD treated with EVT, in 34 hospitals in the Kanto and Kōshin'etsu regions, from August 2014 to August 2016. In total, 2,173 symptomatic patients were followed up for a median of 10.4 months, including 1,370 with claudication, 719 with critical limb ischemia (CLI), and 84 with acute limb ischemia (ALI) for EVT. The all-cause death rates per 100 person-years for claudication, CLI and ALI were 3.5, 26.2, and 24.5, respectively. Similarly, major adverse cardiac and cerebrovascular events (MACCE) rates per 100 person-years for claudication, CLI, ALI, and others were 5.2, 31.2, and 29.7, respectively. After adjusting for the predictors of all-cause death and MACCE, namely, age, body mass index <18, diabetes mellitus, dialysis, cerebrovascular disease, and low left ventricular ejection fraction, it was determined that the preoperative indication for EVT was strongly associated with all-cause death and MACCE.

Conclusions: The preoperative clinical symptoms for EVT can predict the prognosis in patients with PAD undergoing EVT.

Key Words: Acute limb ischemia; Critical limb ischemia; Endovascular therapy; Peripheral artery disease; Prognosis

Despite recent progress in diagnostic procedures and primary prevention techniques, the prevalence of lower limb peripheral artery disease (PAD) has been increasing in recent decades.¹ Several prospective multicenter studies and population-based studies in Western countries and single-center cohort studies in Japan have revealed an unfavorable prognosis for PAD.^{2–4} Therefore,

discussions on how to decrease the global burden of PAD are needed, but to be effective such discussions require accumulation of basic data on patients with PAD. Revascularization is an important strategy for symptomatic chronic refractory claudication or critical limb ischemia (CLI). Novel endovascular therapy (EVT) technologies have been developed for revascularization in patients with

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(Footnote continued the next page.)

PAD.⁵ Additionally, EVT for lower limb arteries has been applied not only to chronic symptomatic disease but also to acute conditions such as acute limb ischemia (ALI). However, previous studies of PAD have only included patients with chronic or acute illness.^{2–4,6–8} Additionally, the only study to investigate the preoperative clinical symptoms for revascularization in patients with PAD was a retrospective single-center study of claudication and CLI.⁹ Prospective cohort studies of patients with PAD who have undergone EVT for all indications, especially patients with ALI, are lacking worldwide. Only 1 prospective multicenter cohort study, which included medical and surgical treatment, was reported from Europe.¹⁰ The present study was performed to clarify whether the preoperative clinical symptoms for EVT can predict post-EVT death and cardiovascular prognosis in Japanese patients with PAD, including those with acute disease, based on a prospective multicenter cohort study.

Methods

Study Design

Toma-Code is the abbreviation for the TOKYO taMA peripheral vascular intervention research COMraDE study. The Toma-Code Registry is a Japanese prospective cohort of consecutive patients with PAD who underwent EVT in 34 hospitals in the Kanto and Kōshin'etsu regions from August 2014 to August 2016. The study protocol was approved by the Ethics Committee at Sakakibara Heart Institute (reference no. 14-023) and the committees at each participating facility. This study was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR No. UMIN000015100).

Study Population

A total of 6 university hospitals, 23 general hospitals, and 5 cardiovascular specialty hospitals participated in this study; 2 facilities performed 1–20 EVT procedures per year, 7 performed 21–50 procedures, 11 performed 51–100 procedures, 7 performed 101–150 procedures, 3 performed 151–200 procedures, 2 performed 201–300 procedures, and 2 performed ≥301 procedures. A total of 2,321 consecutive patients with PAD underwent EVT at these 34 institutes; 83 asymptomatic patients were excluded (e.g., indications for EVT in an asymptomatic patient with PAD were concomitant procedure during endovascular aneurysm repair or preservation of the access route to allow for percutaneous coronary intervention); 67 patients withdrew from the study, and the follow-up rate was 97.1%. Therefore, we finally analyzed the basic data of 2,238 patients and the prognosis of 2,173 patients (Figure 1). The median follow-up period was 10.4 months.

Data Collection and Follow-up Protocol

Demographic, laboratory, angiographic, and procedural data were collected from each patient's hospital chart or from the database by independent researchers according to predetermined definitions, and the study office collectively managed all the data. Follow-up data were obtained from hospital charts or by contacting patients or their family members via telephone. Patients were followed up at 1, 6, 12, 18, and 24 months after EVT.

Endpoints

The major endpoints were all-cause death, cardiovascular death, non-cardiac death, and MACCE (all-cause death, myocardial infarction, and stroke).

A complete listing of the steering committee members and trial investigators in the Toma-Code Registry is provided in the Appendix S1.

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Table 1. Patients' Baseline Characteristics and Comorbidities (n=2,238)

Variable	Total (n=2,238)	Claudication (n=1,399)	CLI (n=750)	ALI (n=89)	P value
Age, years	73.3±9.3	73.0±8.5	73.4±10.5	76.7±11.3	0.0011
Male sex	1,601 (71.5)	1,061 (75.8)	483 (64.4)	57 (64.0)	<0.0001
Systolic BP (mmHg)	137.96±23.29	138.6±21.1	136.5±26.0	140.2±30.2	0.087
Diastolic BP (mmHg)	73.8±14.1	74.4±13.5	72.1±14.4	79.4±18.3	<0.0001
Heart rate (beats/min)	75.5±14.8	73.6±13.5	78.2±15.4	83.5±21.9	<0.0001
ABI right	0.79±0.22	0.79±0.21	0.78±0.25	0.81±0.25	0.695
ABI left	0.77±0.22	0.77±0.21	0.78±0.26	0.75±0.29	0.489
BMI (kg/m ²)	22.4±3.6	22.8±3.4	21.8±4.0	21.6±3.3	<0.0001
<18	195 (8.7)	74 (5.3)	110 (14.7)	11 (12.4)	<0.0001
Hypertension	1,848 (82.6)	1,219 (87.1)	569 (75.9)	60 (67.4)	<0.0001
Dyslipidemia	1,276 (57.0)	900 (64.3)	341 (45.5)	35 (39.3)	<0.0001
Diabetes mellitus	1,271 (56.9)	739 (52.9)	506 (67.5)	26 (29.2)	<0.0001
Diet	227 (10.1)	124 (8.9)	95 (12.7)	8 (9.0)	
Drug	615 (27.5)	383 (27.4)	221 (29.5)	11 (12.4)	
Insulin	429 (19.2)	232 (16.6)	190 (25.3)	7 (7.9)	
Smoking	1,306 (58.4)	897 (64.2)	368 (49.0)	41 (46.1)	<0.0001
Current	510 (22.8)	366 (26.2)	124 (16.5)	20 (22.5)	
Previous	796 (35.6)	531 (38.0)	244 (32.5)	21 (23.6)	
Coronary artery disease	1,061 (47.4)	665 (47.5)	376 (50.1)	20 (22.5)	0.0002
Cerebrovascular disease	325 (14.5)	183 (13.1)	132 (17.6)	10 (11.2)	0.012
Dialysis	610 (27.3)	208 (14.9)	396 (52.8)	6 (6.7)	<0.0001
Heart failure	276 (12.3)	120 (8.6)	143 (19.1)	13 (14.6)	<0.0001
Atrial fibrillation	247 (11.0)	114 (8.1)	105 (14.0)	28 (31.5)	<0.0001
Low LVEF	240 (10.7)	114 (8.1)	121 (16.1)	5 (5.6)	<0.0001
Aortic valve stenosis	49 (2.2)	23 (1.6)	26 (3.5)	0 (0.0)	0.0083
Non-ambulatory status	227 (10.1)	27 (1.9)	186 (24.8)	14 (15.7)	<0.0001
History of major amputation	72 (3.2)	8 (0.6)	60 (7.9)	4 (4.5)	<0.0001
History of EVT in lower extremity	498 (22.3)	288 (20.5)	200 (26.7)	10 (11.2)	0.0061
History of bypass in lower extremity	86 (3.8)	49 (3.5)	34 (4.5)	3 (3.3)	0.575

Data are presented as mean±standard deviation or n (%). ABI, ankle-brachial index; BP, blood pressure; BMI, body mass index; EVT, endovascular therapy.

Definitions

ALI was defined as a sudden decrease in limb perfusion that threatened the viability of the limb and presents within 2 weeks after symptom onset.¹¹ CLI, the most severe clinical manifestation of lower extremity artery disease, was defined as the presence of ischemic rest pain and ischemic lesions or gangrene objectively attributable to arterial occlusive disease.¹² Cardiovascular death included sudden death and death caused by myocardial infarction, stroke, vascular disease, aortic disease, arrhythmia, heart failure, or valvular disease. Non-cardiovascular death was defined as death other than cardiovascular death or death from unknown causes. Non-ambulatory status: the patient requiring a wheelchair or bedridden; low left ventricular ejection fraction (LVEF): <50%; aortic valve stenosis: aortic valve area <1.0cm²; smoking: previous and current smoking; heart failure: history of hospitalization for heart failure or the presence of symptoms of New York Heart Association class III or IV heart failure; and atrial fibrillation: presence of atrial fibrillation on ECG on admission. Other definitions used in this study are shown in **Supplementary Methods**.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation. Categorical data are expressed as number with

percentage. The Kaplan-Meier method was used to calculate survival and MACCE probabilities during the follow-up period. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated using Cox multivariable analysis after adjustment for significant risk factors with P<0.1 in the univariate analysis. The predictors included in the multivariate analysis were the clinical symptoms for EVT, drugs at the time of discharge and patients' basic characteristics, without blood pressure, heart rate, or ankle-brachial index (ABI). All analyses were carried out using SAS software package version 9.4 (SAS Institute, Cary, NC, USA). Individual differences were considered statistically significant at P<0.05.

Results

Patients' Characteristics

The mean age of the 2,238 patients was 73.3 years, and 71.5% of the patients were male. The indications for EVT were classified into 3 groups: claudication (n=1,399, 62.5%), CLI (n=750, 33.5%), and ALI (n=89, 4.0%). The number of patients with diabetes mellitus, smoking, and dialysis was 1,271 (56.9%), 1,306 (58.4%), and 610 (27.3%), respectively. The group with claudication was younger, more predominantly male, had a higher body mass index

Table 2. Drugs at the Time of Discharge (n=2,238)					
Drug	Total (n=2,238)	Claudication (n=1,399)	CLI (n=750)	ALI (n=89)	P value
Aspirin	1,546 (69.1)	1,009 (75.4)	500 (66.7)	37 (41.6)	<0.0001
Thienopyridine	1,511 (67.5)	1,010 (75.4)	471 (62.8)	30 (33.7)	<0.0001
Cilostazol	863 (38.6)	553 (41.3)	284 (37.9)	26 (29.2)	0.15
Eicosapentaenoic acid	196 (8.8)	113 (8.4)	79 (10.5)	4 (4.5)	0.053
Warfarin	269 (12.0)	130 (9.7)	103 (13.7)	36 (40.4)	<0.0001
Direct oral anticoagulant	127 (5.7)	75 (5.6)	33 (4.4)	19 (21.3)	<0.0001
ACEI or ARB	1,192 (53.3)	857 (64.0)	301 (40.1)	34 (38.2)	<0.0001
ACEI	176 (7.9)	129 (9.6)	40 (5.3)	7 (7.9)	0.0068
ARB	1,040 (46.5)	744 (55.6)	269 (35.9)	27 (30.3)	<0.0001
β-blocker	685 (30.6)	432 (32.3)	225 (30.0)	28 (31.5)	0.92
Calcium-channel blocker	1,115 (49.8)	789 (58.9)	295 (39.3)	31 (34.8)	<0.0001
Statin	1,133 (50.6)	819 (61.2)	280 (37.3)	34 (38.2)	<0.0001

Data are presented as n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ALI, acute limb ischemia; AT, angiotensin; CLI, critical limb ischemia.

(BMI) and increased incidence of smoking, hypertension, and dyslipidemia than the other 2 groups. The CLI group had a higher incidence of cerebrovascular disease, dialysis, heart failure, low LVEF, aortic valve stenosis, non-ambulatory status, history of major amputation, and history of EVT in the lower extremity. The ALI group had a higher incidence of atrial fibrillation and lower proportion of coronary artery disease. The patients' characteristics and comorbidities are shown as per preoperative clinical symptoms in **Table 1**.

Drugs at Time of Discharge

Table 2 shows the patients' drug treatments at the time

of discharge. The proportions of patients taking aspirin, thienopyridines, cilostazol, eicosapentaenoic acid (EPA), warfarin, direct oral anticoagulants, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), β-blocker, calcium-channel blocker, and statins at the time of discharge were 69.1%, 67.5%, 38.6%, 8.8%, 12.0%, 5.7%, 53.3%, 30.6%, 49.8%, and 50.6%, respectively. The proportion of patients taking neither aspirin nor thienopyridine and both aspirin and thienopyridine were 10.0% and 47.3%, respectively. The proportion of patients taking aspirin without thienopyridine was 22.1%, which was similar to the proportion of patients taking thienopyridine

without aspirin (20.5%). The proportion of patients in the claudication group taking aspirin, thienopyridines, ACEI or ARB, calcium-channel blocker, or statin was higher.

Kaplan-Meier Curves of All-Cause Death and Freedom From MACCE

Figure 2 shows the Kaplan-Meier curves for overall survival (OS) and MACCE-free survival. The 1-year rates of freedom from all-cause death, cardiovascular death, non-cardiac death, and MACCE were 89.8%, 97.0%, 92.6%, and 87.4% respectively. **Table 3** shows the details of all-cause deaths. The rates of cardiovascular death, infectious disease-related death, and malignancy-related death were 28.1%, 34.2%, and 8.0%, respectively.

Predicted Risk for All-Cause Death and MACCE in Cox Multivariable Analysis

The results of the Cox multivariable analysis of the individual patients' characteristics, comorbidities, and drug treatments at the time of discharge associated with each factor are shown in **Table 4** and **Table S1**. Age, BMI <18 kg/m², diabetes mellitus, dialysis, cerebrovascular disease, low LVEF, ALI, CLI, ACEI or ARB administration, and aspirin administration were independent predictors of all-cause death. Age, BMI <18, diabetes mellitus, dialysis, cerebrovascular disease, low LVEF, atrial fibrillation, ALI, and CLI were independent predictors of MACCE.

Indications for EVT

The Kaplan-Meier curves for all-cause death and MACCE-free survival according to the preoperative clinical symptoms for EVT are shown in **Figure 3**, which indicates that the event rates of all-cause death and MACCE were significantly higher in patients with CLI and ALI than in patients with claudication. **Table 5** shows all-cause death, cardiac death, non-cardiac death, and MACCE event rates per 100 person-years, after adjusting for the potential confounding factors shown in **Table 4** using the Cox proportional hazards model. It also shows the adjusted HRs for all-cause death, cardiovascular death, non-cardiovascular death, and MACCE according to the preoperative clinical symptoms. For patients with claudication, CLI, and ALI, the 1-year OS rates were 97%, 76%, and 84%, respectively, and the all-cause death event rates per 100 person-years were 3.5, 26.2, and 24.5, respectively. Similarly, the 1-year MACCE-free rates in patients with claudication, CLI and ALI were 95%, 72%, and 81%, respectively, and the MACCE event rates per 100 person-years were 5.2, 31.2, and 29.7, respectively. The event rate of all-cause death adjusted for potential confounding factors was significantly higher in patients with CLI (HR: 3.74 [95% CI: 2.54–5.50]) and ALI (HR: 4.27 [95% CI: 2.17–8.41]) than in patients with claudication. Additionally, the event rate of MACCE was significantly higher in patients with CLI and ALI than in patients with claudication (HR: 3.05 [95% CI: 2.18–4.26] and HR: 3.66 [95% CI: 2.00–6.69]). There were no statistically significant differences in the event rates of all-cause death, cardiac death, non-cardiac death, and MACCE between patients with CLI and those with ALI. The event rate of cardiovascular death was significantly higher in patients with CLI (HR: 3.04 [95% CI: 1.51–6.13]) than in patients with claudication. Furthermore, the event rate of non-cardiovascular death was significantly higher in patients with CLI (HR: 4.57 [95% CI: 2.90–7.19])

Table 3. Causes of Death (n=199)

Cardiovascular death	56 (28.1)
Heart failure	22 (11.1)
Ventricular fibrillation and sudden death	13 (6.5)
Acute myocardial infarction	7 (3.5)
Stroke	7 (3.5)
Infarction	5 (2.5)
Bleeding	2 (1.0)
Aortic valve stenosis	1 (0.5)
Aortic disease	2 (1.0)
ALI	1 (0.5)
CLI	2 (1.0)
Bradycardia	1 (0.5)
Non-cardiovascular death	143 (71.6)
Infection	68 (34.2)
Pneumonia	36 (18.1)
Sepsis	27 (13.6)
Colitis	2 (1.0)
Other	3 (1.5)
Malignancy	16 (8.0)
Multiple organ failure	8 (4.0)
Bleeding	8 (4.0)
Renal failure	8 (4.0)
Senility	3 (1.5)
Ileus	3 (1.5)
Non-occlusive mesenteric ischemia	2 (1.0)
Blue toe syndrome	1 (0.5)
Bone marrow disease	1 (0.5)
Respiratory failure	1 (0.5)
Chronic obstructive pulmonary disease	1 (0.5)
Liver failure	1 (0.5)
Hyperkalemia	1 (0.5)
Suffocation	2 (1.0)
Unknown	19 (9.5)

Data are presented as n (%). ALI, acute limb ischemia; CLI, critical limb ischemia.

and ALI (HR: 5.30 [95% CI: 2.52–11.16]) than in patients with claudication.

Discussion

This multicenter prospective cohort registry included not only patients with claudication or CLI but also those with ALI. This is the first prospective multicenter study in Japan to analyze such patients simultaneously.

Patients' Characteristics and Comorbidities

Diabetes mellitus is an important risk factor for PAD.¹³ Patients who are undergoing dialysis and develop PAD have a poor prognosis.^{3,6} In the present study, 56.9% of patients had diabetes mellitus and 27.3% were undergoing dialysis; these rates are higher than those in a previous report (38.8% and 4.9%, respectively).¹⁴ The rate of atrial fibrillation was 10.8%, which is similar to that in a previous study of patients with PAD requiring hospitalization (13.4%).¹⁵

Table 4. Predicted Risk for All-Cause Death and MACCE in Cox Multivariable Analysis				
	Reference	HR	95% CI	P value
All-cause death				
Age				
10-year increase		1.49	1.27–1.76	<0.0001
BMI				
<18		1.92	1.32–2.79	0.0006
Diabetes mellitus		1.39	1.00–1.93	0.047
Dialysis		2.50	1.80–3.48	<0.0001
Heart failure		1.42	0.98–2.07	0.0628
Cerebrovascular disease		1.72	1.22–2.43	0.002
Low LVEF		2.23	1.50–3.32	<0.0001
Clinical symptoms				
Claudication				
ALI		4.27	2.17–8.41	<0.0001
CLI		3.74	2.54–5.50	<0.0001
Aspirin		0.65	0.47–0.90	0.010
Thienopyridine		0.74	0.54–1.02	0.062
Cilostazol		0.73	0.52–1.02	0.064
ACEI or ARB		0.63	0.46–0.86	0.0036
MACCE				
Age				
10-year increase		1.37	1.18–1.59	<0.0001
BMI				
<18		1.79	1.26–2.55	0.0013
Diabetes mellitus		1.43	1.07–1.92	0.015
Dialysis		2.45	1.83–3.28	<0.0001
Cerebrovascular disease		1.65	1.21–2.24	0.0014
Atrial fibrillation		1.42	1.01–1.99	0.046
Non-ambulatory status		1.34	0.97–1.85	0.078
Low LVEF		2.28	1.65–3.14	<0.0001
Clinical symptoms				
Claudication				
ALI		3.66	2.00–6.69	<0.0001
CLI		3.05	2.18–4.26	<0.0001
Aspirin		0.75	0.55–1.01	0.062
Thienopyridine		0.78	0.58–1.04	0.087
Cilostazol		0.77	0.57–1.05	0.099

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction. Other abbreviations as in Tables 1,2.

Drug Treatments

According to data from the Heart Protection Study,¹⁶ statin therapy not only reduces the risk of cardiovascular events but also improves limb outcomes. However, the rate of statin administration in the present study was only 50.6%, which is lower than in a previous study of patients with claudication¹⁷ and more than in a previous study of patients with CLI.¹⁸ Another previous study showed that statin treatment was not effective for patients undergoing dialysis.¹⁹ Because patients undergoing dialysis constituted 27.3% of the patients in the present study, the rate of statin administration might have been low. With respect to antithrombotic therapy after EVT, previous authors have recommended aspirin monotherapy or dual antiplatelet therapy after EVT.²⁰ In fact, aspirin administration was an independent significant predictive factor for all-cause death. In the present study, the rates of aspirin administration without thienopyridine (22.1%) and dual antiplatelet therapy (47.3%) were low. It can be presumed that only

thienopyridines (20.5%) may be used as a single agent instead of aspirin. As reported by Iida et al,²¹ cilostazol can reduce the restenosis rate in superficial femoral artery lesions, and the rate of cilostazol administration in the present study was 38.1%. However, cilostazol can cause tachycardia, and β -blockers decrease the heart rate. The 38.1% rate of cilostazol administration and 30.6% rate of β -blocker administration in this study resulted in an average heart rate of 75.5 beats/min, which was relatively controlled. Subanalysis of the JELIS trial demonstrated that EPA could reduce coronary artery events in PAD patients.²² In the present study, the rate of EPA administration in the patients with CLI was 10.5% and higher than in the previous study.¹⁸ In this study, ACEI or ARB administration were both significantly predictive factors for all-cause death, similar to a previous report in Japan.²³ Long-term oral anticoagulation therapy is indicated in patients with acute thrombosis of a native artery associated with thrombophilia and in those with cardiac embolism.¹¹ In the present study,

Figure 3. Kaplan-Meier estimates of (A) freedom from all-cause death and (B) freedom from major adverse cardiac and cerebrovascular events (MACCE) according to preoperative clinical symptoms.

Table 5. Cox Proportional Hazards Models of All-Cause Death, MACCE, Cardiovascular Death, and Non-Cardiovascular Death According to Preoperative Clinical Symptoms

	Patients (n)	Events (n)	Event rate (n/100pt.-year)	HR	95% CI	P value	HR	95% CI	P value
All-cause death									
Claudication	1,370	44	3.5		Ref.				
CLI	719	139	26.2	3.74	2.54–5.50	<0.0001		Ref.	
ALI	84	16	24.5	4.27	2.17–8.41	<0.0001	1.14	0.60–2.18	0.690
Cardiovascular death									
Claudication	1,370	14	1.1		Ref.				
CLI	719	38	7.2	3.04	1.51–6.13	<0.0001		Ref.	
ALI	84	4	6.1	2.72	0.70–10.60	<0.0001	0.90	0.24–3.32	0.897
Non-cardiovascular death									
Claudication	1,370	30	2.4		Ref.				
CLI	719	101	19.0	4.57	2.90–7.19	<0.0001		Ref.	
ALI	84	12	18.3	5.30	2.52–11.16	<0.0001	1.16	0.58–2.34	0.678
MACCE									
Claudication	1,370	66	5.2		Ref.				
CLI	719	163	31.2	3.05	2.18–4.26	<0.0001		Ref.	
ALI	84	19	29.7	3.66	2.00–6.69	<0.0001	1.14	0.60–2.18	0.690

Adjusted for age, sex, smoking, diabetes mellitus, hypertension, dyslipidemia, dialysis, heart failure, coronary artery disease, cerebrovascular disease, atrial fibrillation, non-ambulatory status, low LVEF, and aortic valve stenosis. MACCE, major adverse cardiac and cerebrovascular events. Other abbreviations as in Tables 2,4.

the rates of embolism and thrombophilia in a native artery in the ALI patients were 31.5% and 45.0%, respectively. We should have prescribed anticoagulation treatment for both embolism and thrombophilia in a native artery. However, as a result, the rate of anticoagulant administration was relatively low at approximately 60% combined warfarin

and direct oral anticoagulant. This might affected the poor prognosis in the ALI patients.

Prognosis

The 1-year OS rate in this Japanese study was 90%, which is worse than in a previous Japanese study ($\approx 95\%$) of PAD

after EVT.^{23,24} We presume that selection bias resulted in the exclusion of patients with a poorer prognosis in the previous study, such as those who had undergone unsuccessful EVT, ALI, and CLI with a Rutherford classification of 6. In the present study, the rate of cardiovascular death was only 28.1%, which is lower than in a previous PAD registry ($\approx 50\%$) in which 10–20% of patients had CLI and approximately 6% were undergoing dialysis.^{4,6} Additionally, unknown causes of death (9.5%) were included as non-cardiac deaths in the present study. In a retrospective multicenter study of patients who underwent EVT for femoropopliteal lesions, Soga et al¹⁴ reported differences in the causes of death between patients with claudication and those with CLI. They found that infections such as pneumonia and sepsis were more frequent in patients with CLI than in patients with claudication. Additionally, cardiovascular death was more frequent in patients with claudication than in those with CLI. Iida et al reported that the rates of cardiac death, including cerebrovascular death and infectious death, were 27.8% and 42.6% in their study targeting patients with CLI undergoing EVT.²⁵ Furthermore, the rate of death caused by infectious disease is substantially higher in patients undergoing hemodialysis than in the general population.²⁶ One study showed that a non-ambulatory status could significantly predict worse deaths in patients with pneumonia.²⁷ Therefore, low rates of cardiovascular death and high rates of infectious death are reasonable results considering the inclusion of relatively large numbers of patients with a non-ambulatory status (10.1%), CLI (33.5%), and dialysis (27.3%) in this study.

Preoperative Clinical Symptoms

The 1-year OS rate of patients with claudication was 97%, which is slightly better than in a previous study by Kumakura et al (94.5%).⁴ We presume that the cause of this better clinical outcome is the difference in the patients' treatment entry time, which was dependent upon the time period of each study (1990–2007 in the study by Kumakura et al⁴ and 2014–16 in the present study). The 1-year OS rate of patients with CLI was 76%, which is similar to that in the studies by Kumakura et al⁴ (72.7%) and Iida et al²¹ (80.0%). Patients with CLI had a poor prognosis and some differences according to lesion location, such as the aortoiliac artery or femoropopliteal artery.^{13,14,20} In the present study, the rate of comorbidities such as diabetes mellitus, non-ambulatory status, dialysis, heart failure, aortic valve stenosis, and low LVEF for a poor prognosis in patients with CLI was higher than that in the other 2 groups. Thus, it is comprehensible that patients with CLI have a poor prognosis. The 1-year OS rate in patients with ALI was 84%, which is the same as in a previous report after EVT (84%).⁸ In patients with ALI, the performance of EVT, including catheter direct thrombolysis, has given good limb salvage results similar to those after surgical procedures for ALI during the past 2 decades.^{8,11} However, some studies targeting only patients with ALI have shown unfavorable mortality rates in these patients; in particular, a perioperative mortality rate associated with revascularization strategies of approximately 5–9%.^{7,8,11} Additionally, in the present study, the perioperative mortality rate associated with EVT in patients with ALI was high at approximately 10% and worst among all indications (**Figure 3**). Surgical thromboembolectomy is a useful and simple method for ALI caused by embolism. However, there was the possibility that EVT was selected in surgical thromboembolectomy-appropriate

cases. Because the criteria for selecting the revascularization strategy for ALI patients were different among the facilities in this study, this might have affected the poor prognosis for ALI patients. Furthermore, patients with ALI were the oldest among all the patient groups. In the present study, the rate of comorbidities such as a non-ambulatory status, BMI <18, heart failure, and atrial fibrillation for a poor prognosis in patients with ALI was higher than in the patients in the claudication group. Furthermore, the proportion of ALI patients in this registry was lower (4.0%) than in a previous study (9.5%) using the COPART registry.¹⁰ It is possible that most of the ALI patients with fewer comorbidities were treated surgically and those with substantial comorbidities and high perioperative risks were included in this study. In this respect, the poor prognosis of the patients of ALI is reasonable. Considering this, we should prescribe oral anticoagulation for all ALI patients with a native artery not only for embolic ALI patients and carefully watch to avoid bleeding events. Furthermore, if possible, we should consider ACEI or ARB administration for improving the prognosis of ALI patients. The Cox multivariable analysis indicated that CLI and ALI were stronger predictors for all-cause death and MACCE than was claudication. Clinicians should recognize that patients with all preoperative clinical symptoms except for claudication have poor mortality rates and a fair cardiovascular prognosis. Furthermore, simply considering the patient's preoperative clinical symptoms prior to performing the intervention could allow for adjustment of the strength of the intervention during and after EVT by predicting death and the cardiovascular prognosis. For example, the follow-up intervals after EVT should be shorter in patients with CLI than in those with claudication, and aspirin, ACEI, or ARB as demonstrated in this study can be selected for improvement of the cardiovascular prognosis in patients undergoing medical treatment. Further studies are needed to clarify which treatments improve the prognosis in patients with each preoperative clinical symptom.

Study Limitations

This study had 6 main limitations. First, some patients may not have been enrolled because of an unwillingness to participate or for other reasons. However, we believe that the selection bias in this study was minimal. Second, the current study included only Japanese patients. Whether the results can be applied to patients of other ethnicities is unclear. Third, patients treated only with a surgical revascularization strategy or medical strategy were not included in this study. Fourth, the criteria for selecting the revascularization strategy for ALI patients differed among the facilities in this study. This selection bias might have affected the prognosis of the ALI patients. Fifth, the success rate of EVT was excluded from our analysis. Although a patient might have multiple EVT and lesions, this study analysis was based only on the patients, not accounting for the multiple EVT procedures and multiple lesions. Therefore, to define successful EVT was very difficult. Furthermore, the success rate of EVT is mainly involved in limb prognosis. Finally, the follow-up period was short.

Conclusions

Preoperative clinical symptoms for EVT can be used to predict the prognosis in patients with PAD undergoing EVT.

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Conflict of Interest

None declared.

References

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. 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. Reinecke H, Unrath M, Freisinger E, Bunzemeier H, Meyborg M, Lüders F, et al. Peripheral arterial disease and critical limb ischaemia: Still poor outcomes and lack of guideline adherence. *Eur Heart J* 2015; **36**: 932–938.
3. Diehm C, Allenberg JR, Pittrow D, Mahn M, Tepohl G, Haberl RL, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation* 2009; **120**: 2053–2061.
4. Kumakura H, Kanai H, Aizaki M, Mitsui K, Araki Y, Kasama S, et al. 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.
5. Kullo IJ, Rooke TW. Clinical Practice: Peripheral artery disease. *N Engl J Med* 2016; **374**: 861–871.
6. Kumakura H, Kanai H, Araki Y, Hojo Y, Iwasaki T, Ichikawa S. 15-Year patency and life expectancy after primary stenting guided by intravascular ultrasound for iliac artery lesions in peripheral arterial disease. *JACC Cardiovasc Interv* 2015; **8**: 1893–1901.
7. Eliason JL, Wainess RM, Proctor MC, Dimick JB, Cowan JA Jr, Upchurch GR Jr, et al. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. *Ann Surg* 2003; **238**: 382–390.
8. Byrne RM, Taha AG, Avgerinos E, Marone LK, Makaroun MS, Chaer RA. Contemporary outcomes of endovascular interventions for acute limb ischemia. *J Vasc Surg* 2014; **59**: 988–995.
9. Taylor SM, Cull DL, Kalbaugh CA, Senter HF, Langan EM, Carsten CG, et al. Comparison of interventional outcomes according to preoperative indication: A single center analysis of 2,240 limb revascularizations. *J Am Coll Surg* 2009; **28**: 770–780.
10. Cambou JP, Aboyans V, Constans J, Lacroix P, Dentans C, Bura A. Characteristics and outcome of patients hospitalised for lower extremity peripheral artery disease in France: The COPART Registry. *Eur J Vasc Endovasc Surg* 2010; **39**: 577–585.
11. Creager MA, Kaufman JA, Conte MS. Acute limb ischemia. *N Engl J Med* 2012; **366**: 2198–2206.
12. European Stroke Organisation, Tenders M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, et al; ESC Committee for Practice Guidelines. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32**: 2851–2906.
13. Beckman JA, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part II. *Eur Heart J* 2013; **34**: 2444–2456.
14. Sigvant B, Kragsterman B, Falkenberg M, Hasvold P, Johansson S, Thuresson M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J Vasc Surg* 2016; **64**: 1009–1017.
15. Wasmer K, Unrath M, Köbe J, Malyar NM, Freisinger E, Meyborg M, et al. Atrial fibrillation is a risk marker for worse in-hospital and long-term outcome in patients with peripheral artery disease. *Int J Cardiol* 2015; **199**: 223–228.
16. 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.
17. Aihara H, Soga Y, Mii S, Okazaki J, Yamaoka T, Kamoi D, et al. Comparison of long-term outcome after endovascular therapy versus bypass surgery in claudication patients with Trans-Atlantic Inter-Society Consensus-II C and D femoropopliteal disease. *Circ J* 2014; **78**: 457–464.
18. Soga Y, Mii S, Aihara H, Kuma S, Okazaki J, Yamaoka T, et al. Comparison of clinical outcome after bypass surgery vs. endovascular therapy in patients with critical limb ischemia. *Circ J* 2013; **77**: 2102–2109.
19. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al; the AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009; **360**: 1395–1407.
20. Sobieszczyk P, Eisenhauer A. Management of patients after endovascular interventions for peripheral artery disease. *Circulation* 2013; **128**: 749–757.
21. Iida O, Yokoi H, Soga Y, Inoue N, Suzuki K, Yokoi Y, et al; STOP-IC Investigators. Cilostazol reduces angiographic restenosis after endovascular therapy for femoropopliteal lesions in the Sufficient Treatment of Peripheral Intervention by Cilostazol study. *Circulation* 2013; **127**: 2307–2315.
22. Ishikawa Y, Yokoyama M, Saito Y, Matsuzaki M, Origasa H, Oikawa S, et al; JELIS Investigators, Japan. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral artery disease. *Circ J* 2010; **74**: 1451–1457.
23. Soga Y, Iida O, Kawasaki D, Yamauchi Y, Suzuki K, Hirano K, et al; REAL-AI Investigators. Contemporary outcomes after endovascular treatment for aorto-iliac artery disease. *Circ J* 2012; **76**: 2697–2704.
24. 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.
25. Iida O, Nakamura M, Yamauchi Y, Kawasaki D, Yokoi Y, Yokoi H, et al; OLIVE Investigators. Endovascular treatment for infrainguinal vessels in patients with critical limb ischemia: OLIVE registry, a prospective, multicenter study in Japan with 12-month follow-up. *Circ Cardiovasc Interv* 2013; **6**: 68–76.
26. Wakasugi M, Kawamura K, Yamamoto S, Kazama JJ, Narita I. High mortality rate of infectious disease in dialysis patients: A comparison with general population in Japan. *Ther Apher Dial* 2012; **16**: 226–231.
27. Shido Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Goto Y, et al; Central Japan lung study group. Risk factors for 30-day mortality in patients with pneumonia who receive appropriate initial antibiotics: An observational cohort study. *Lancet Infect Dis* 2015; **15**: 1055–1065.

Supplementary Files

Supplementary File 1

Appendix S1. Toma-Code Registry Committee

Supplementary Methods

Table S1. Predicted risk of cardiovascular death and non-cardiovascular death in Cox multivariable analysis

Please find supplementary file(s);
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