Original Article

Optimal Strategy for Antiplatelet Therapy in Patients With Lower Extremity Artery Disease

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ABSTRACT

Background: The duration of antiplatelet therapy in patients with lower extremity artery disease (LEAD) has not been well established. This study aimed to evaluate the clinical outcome according to the duration of dual-antiplatelet therapy (DAPT).

Methods: From April 2009 through June 2019, 376 patients with LEAD underwent successful endovascular revascularization. After the procedure, the received single-antiplatelet therapy (SAPT) or DAPT of various durations were classified into 2 groups (SAPT or DAPT < 6 months vs DAPT ≥ 6 months). The primary outcomes were major adverse cardiovascular events (MACE) and major adverse limb events (MALE). The safety outcome was moderate-to-severe bleeding according to the Global Use of Strategies to Open Occluded Arteries (GUSTO) criteria.

Results: Over the 40-month follow-up period, MACE occurred less frequently in the DAPT ≥ 6-month group than in the SAPT or DAPT < 6-month group (12.4% vs 23.8%; hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.35 to 0.89; *P* = 0.014) after inverse probability-weighted adjustment and propensity-score matching analysis (HR, 0.55, 95% CI, 0.30 to 0.99, *P* = 0.048). MALE showed no significant differences between the 2 groups (DAPT ≥ 6-month group: 17.1% vs SAPT or DAPT < 6-month group: 13.1%; HR, 1.05; 95% CI, 0.62 to 1.78; *P* = 0.846). A significant difference between the DAPT ≥ 6-month group and the SAPT or DAPT < 6-month group was not observed regarding the incidence of moderate-to-severe GUSTO bleeding.

Conclusions: In patients with LEAD, DAPT for ≥ 6 months after endovascular revascularization was associated with a lower incidence of MACE. ***(Iranian Heart Journal 2024; 25(1): 42-55)***

KEYWORDS: Peripheral artery disease, Lower extremity artery disease, Endovascular revascularization, Antiplatelet therapy

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Peripheral artery disease (PAD) is an advanced form of atherosclerosis. Lower extremity artery disease (LEAD) is one of the subtypes of PAD. Patients with LEAD can present with symptoms varying from intermittent claudication to critical limb ischemia (CLI). [1, 2] Owing to the fact that it is highly likely for patients with LEAD to be accompanied by coronary artery disease (CAD) and carotid artery disease, they are at

an elevated risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction (MI), and stroke, and limb events, such as amputation and repeat revascularization. [2, 3] Patients with LEAD who have undergone endovascular revascularization show more advanced atherosclerosis. Antiplatelet agent administration is the mainstay of treatment after revascularization. [4, 5] Dual-antiplatelet therapy (DAPT) may be reasonable to reduce the risk of MACE and major adverse limb events (MALE) after lower extremity revascularization in patients with symptomatic LEAD. [6] Although recent guidelines recommend 1-month DAPT after lower extremity interventions, data specifying the appropriate period beyond the 1-month treatment are insufficient. [7, 8] Peter et al [9] reported that DAPT at discharge was associated with prolonged survival in patients with CLI undergoing revascularization, and Cho et al [10] reported that DAPT ≥ 6 months was associated with decreased MACE in patients with PAD. Nonetheless, in comparison with coronary artery interventions, data for the duration of DAPT after lower extremity artery endovascular revascularization are insufficient. Therefore, this study aimed to determine an appropriate period of DAPT after endovascular revascularization for patients with LEAD and investigate the clinical outcomes, including the incidence of MACE and MALE and the bleeding risk, during antiplatelet agent therapy.

METHODS

Participants and Study Design

Between April 2009 and June 2019, 461 patients diagnosed clinically with PAD who received invasive vascular treatment at Sanggye Paik Hospital in Seoul, South Korea, were included in this study. We excluded patients with combined bypass surgery or aortic interventions, including endovascular aortic aneurysm repair, and patients with anticoagulation medication, including warfarin and new oral anticoagulants. Moreover, 85 patients were excluded for the following reasons: non-atherosclerotic disease (n = 8), incomplete data (including drug history [n = 35]), non-endovascular therapy (n = 16), and loss to follow-up before 6 months (n = 26). Nevertheless, patients who had cardiovascular events before 6 months were included in the analysis. A total of 376 patients with symptomatic LEAD (claudication or CLI) were included in the study. The study protocol was approved by the Institutional Review Board at Sanggye Paik Hospital (2021-08-006).

Data were collected from the patients' electronic medical records and angiography findings. The Rutherford classification was used; claudication was classified into categories 1–3 (mild, moderate, and severe claudication, respectively), while CLI was classified into categories 4–6 (ischemic rest pain, minor tissue loss, and major tissue loss, respectively). The drug prescriptions administered before endovascular treatment and during follow-up were verified. Patients whose antiplatelet agents were changed following a prescription at discharge or during the 3-month follow-up were excluded from the final analysis. For the included patients, the prescription on discharge was considered. Patients were categorized into 2 groups (DAPT < 6 months or SAPT vs DAPT ≥ 6 months). SAPT was defined as taking aspirin (100 mg/d) or clopidogrel (75 mg/d), while DAPT was defined as taking aspirin (100 mg/d) plus clopidogrel (75 mg/d).

Endovascular Treatment

All the patients were given aspirin and clopidogrel 7 days before the procedure or were loaded with aspirin (300 mg) and clopidogrel (300 mg) 1 day before the procedure. The duration of DAPT after the procedure was left to the physician's

discretion. Most of the puncture sites were achieved via a femoral approach, and either a contralateral or an ipsilateral approach was taken depending on the location of the lesion. When the sheath was inserted after the puncture, 5000 IU of heparin was administered as an intra-arterial bolus. For target lesion treatment, wiring was attempted with 0.035-, 0.018-, and 0.014-inch guide wires, and intraluminal and subintimal tracking was attempted depending on the situation. After wiring, balloon angioplasty and stent insertion were performed, and this was left to the operator's discretion. Drug-eluting stents were not available during the period of the index procedures.

Data Collection and Follow-Up

Clinical and outcome data were collected from electronic medical records. Congestive heart failure was defined as an ejection fraction below 40% using the biplane Simpson method in transthoracic echocardiography. CAD was defined as the presence of significant stenosis (luminal narrowing ≥ 50% in any coronary artery with the reference diameter) in angiography or computed tomography. Additionally, previous cardiovascular disease (CVD) history, including MI, and previous angioplasty were included.

The variables evaluated during the endovascular procedure included the target lesion, Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease classification (TASC; TASC I: infrapopliteal level; and TASC II: aortoiliac and femoropopliteal levels), [11] the number of diseased vessels, the intervention type (balloon angioplasty, atherectomy, or stent insertion), and the pre- and post-intervention ankle-brachial index (ABI). Multilevel disease was defined as the presence of significantly obstructed lesions at > 1 level in the same limb. In the case of multilevel disease, the TASC classification was defined as a target lesion requiring intervention, and in the case of multi-level intervention, the TASC classification was defined as a lesion with worse TASC classification. In cases with bilateral PAD, we included the first treated limb as an index procedure. Follow-up examinations, including a physical examination, were conducted at 2 weeks postoperatively and then at intervals of 1–3 months. During follow-up, an additional imaging test was performed in the event of symptom exacerbation, limb color change, or decreased ABI > 0.2. Furthermore, repeated intervention was performed at the decision of the operator.

Clinical Outcomes

The primary endpoints were the incidence of MACE (a composite occurrence of all-cause death, MI, and stroke) and MALE (a composite occurrence of unplanned repeat revascularization and major amputation). [12] Repeat revascularization was defined as repeated intervention or bypass surgery on the target limb, and major amputation was defined as above-the-ankle amputation of the index limb. If the patient had multiple events, we classified the first event as MACE or MALE. The safety outcome was moderate-to-severe bleeding according to the Global Use of Strategies to Open Occluded Arteries (GUSTO) criteria. Among patients receiving DAPT, if the event occurred before 6 months, it was judged as the SAPT or DAPT < 6-month group. Severe bleeding was defined as intracerebral hemorrhage that resulted in hemodynamic compromise necessitating treatment, and moderate bleeding was defined as a situation requiring blood transfusion but not resulting in hemodynamic compromise. [13] Experienced attending physicians diagnosed all events, and 3 cardiologists reviewed the angiographic findings.

Statistical Analysis

The χ^2 or Fisher exact test was used to compare categorical variables, which were

reported as numbers (percentages). The Student *t* test was used to compare continuous variables, and the mean and standard deviation values were obtained. A Kaplan–Meier survival analysis was used to compare the 3-year event rates. Hazard ratios (HRs) were calculated using a Cox regression analysis. Univariate and multivariate analyses were applied to determine the predictors of clinical outcomes. HRs were provided with 95% confidence intervals (CIs). For all tests, a *P* value < 0.05 was considered significant. All the statistical analyses were performed with the Statistical Package for the Social Sciences for Windows, release 25.0 (IBM Corp, Armonk, NY, USA). To compare the clinical influence of differences in duration between the antiplatelet groups and reduce the effect of selection bias and potential confounding between the 2 groups, we used propensity score-matching (PSM) and inverse probability treatment weighting (IPTW) using propensity scores (PSs) on the basis of the demographic, laboratory, and treatment characteristics of the patients. [14] The following 22 variables were commonly used as matching variables for IPTW and PSM: age, sex, CLI, hypertension, diabetes, dyslipidemia, heart failure, chronic kidney disease, CAD, stroke, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, statin therapy, smoking status, body mass index, hemoglobin level, serum albumin level, low-density lipoprotein level, TASC classification, target lesion, procedure type, and index procedure year. The propensity score was used to balance covariates between the 2 groups to reduce the biasing effects of between-group differences in baseline characteristics. The nearest neighbor matching method and the 1:1 matching algorithm without replacement were used to select a match. To measure the balancing, we calculated the standardized bias for each measured covariate for the weighted samples. The SAS software (version 9.4) was used for the IPTW analysis. This software automatically computes the PS scores and conducts a balance check using a generalized boosted regression. Multivariate Cox regression analysis was performed using variables employed in the propensity score matching mentioned above. Variables with a *P* value < 0.05 in the univariate analysis were included in the final multivariate analysis.

RESULTS

Baseline Characteristics

The study population underwent follow-up for a mean duration of 37 months. Among the 376 patients, 206 received DAPT < 6 months or SAPT and 170 received DAPT ≥ 6 months. The baseline clinical characteristics of the study population are shown in Supplemental Table 1. The 2 groups showed no significant differences in sex, body mass index, smoking history, and the prevalence of hypertension, diabetes mellitus, chronic kidney disease, congestive heart failure, CAD, previous MI, previous stroke, and previous percutaneous transluminal angioplasty. Patients in the DAPT ≥ 6-month group were younger; had a high prevalence of dyslipidemia; were prescribed aspirin, clopidogrel, and statin at a higher rate; and showed high levels of hemoglobin, low-density lipoprotein, and albumin in the laboratory assessments.

The 2 groups exhibited no significant differences in the incidence of multilevel disease and TASC classification (Supplemental Table 2). However, the proportion of patients with CLI was higher in the DAPT < 6-month or SAPT group than in the DAPT ≥ 6-month group. Moreover, targeting for below-the-knee lesions was more frequent in the DAPT < 6-month or SAPT group. Stent insertion was performed more frequently in the DAPT ≥ 6-month group. The frequency of atherectomy-device

usage during the procedure was similar in both groups (the DAPT < 6-month or SAPT group = 5.8% vs the DAPT ≥ 6-month group = 4.7%; *P* = 0.802). The ABI measured before and after the procedure showed no significant difference between the 2 groups.

Clinical Outcomes According to DAPT Duration

Clinical outcomes in the DAPT < 6-month or SAPT group and the DAPT ≥ 6-month group are shown in Supplemental Table 3 and Table 2, respectively. MACE was lower in the DAPT ≥ 6-month group (event rate = 12.4% vs 23.8% and annual incidence = 0.033 vs 0.086; *P* = 0.001). Moreover, the incidence of all-cause death was lower in the DAPT ≥ 6-month group (event rate = 8.2% vs 20.4% and annual incidence = 0.022 vs 0.071; *P* = 0.001). Still, the incidence of MI (2.4% vs 1.0%) and stroke (1.8% vs 2.9%) did not differ significantly between the 2 groups. The incidence of moderate-to-severe bleeding or severe bleeding was also not different between the 2 groups.

Analysis of Clinical Outcomes According to DAPT Duration

We performed multivariate Cox regression analysis to adjust for age, congestive heart failure, chronic kidney disease, CLI, and TASC classification to evaluate the association between DAPT duration and MACE. In the multivariate Cox regression analysis, DAPT ≥ 6 months was associated with lower MACE (HR, 0.54; 95% CI, 0.31 to 0.94; *P* = 0.030). Nonetheless, it did not show statistical significance for the incidence of MALE (HR, 1.04; 95% CI, 0.60 to 1.81; *P* = 0.885) and moderate-to-severe bleeding (Supplemental Table 4).

Analysis Before and After IPTW and PSM

We performed IPTW and PSM according to DAPT duration. We used variables including age, sex, CLI, hypertension, diabetes dyslipidemia, heart failure, chronic kidney disease, CAD, stroke, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, statin therapy, smoking status, body mass index, hemoglobin level, serum albumin level, low-density lipoprotein level, TASC classification, target lesion, procedure type, and index procedure year. The baseline characteristics of the study population after IPTW are presented in Table 1 and Supplemental Table 5.

MACE was lower in the DAPT ≥ 6-month group (HR, 0.42; 95% CI, 0.25 to 0.71; *P* < 0.001) (Table 2). The incidence of all-cause death was also lower in the DAPT ≥ 6-month group (HR, 0.34; 95% CI, 0.18 to 0.62; *P* < 0.001). However, the incidence of MALE (HR, 1.03; 95% CI, 0.61 to 1.76; *P* = 0.91) did not differ significantly between the 2 groups. Regarding the bleeding event, neither moderate-to-severe bleeding nor severe bleeding showed any difference between the 2 groups.

The clinical benefit of DAPT ≥ 6 months was also consistent after IPTW adjustment. MACE occurred less frequently in the DAPT ≥ 6-month group than in the DAPT < 6-month or SAPT group (HR, 0.56; 95% CI, 0.35 to 0.89; *P* = 0.014). Additionally, all-cause death occurred less frequently in the DAPT ≥ 6-month group (HR, 0.52; 95% CI, 0.32 to 0.86; *P* = 0.011). The MALE rate was similar between the 2 groups (HR, 1.03; 95% CI, 0.61 to 1.76; *P* = 0.905), and IPW adjustment also showed no significant difference between the 2 groups (HR, 1.05; 95% CI, 0.62 to 1.78; *P* = 0.846). In the assessment of bleeding events, moderate-to-severe GUSTO bleeding showed no significant difference between the 2 groups (HR, 0.84; 95% CI, 0.35 to 2.03; *P* = 0.703), and severe GUSTO bleeding showed no difference between the 2 groups (HR, 1.62; 95% CI, 0.29 to 8.96; *P* = 0.583) after IPTW adjustment. A similar pattern was also

shown after PSM analysis. Both MACE (HR, 0.55; 95% CI, 0.30 to 0.99; *P* = 0.048) and death (HR, 0.50; 95% CI, 0.24 to 1.00; *P* = 0.053) occurred less frequently in the DAPT ≥ 6-month group.

Furthermore, the Kaplan–Meier curve showed a decreased MACE rate in the prolonged DAPT group (Fig. 1) before and after IPTW matching and no difference in terms of MALE or moderate-to-severe bleeding event (Fig. 2).

Table 1: Baseline Characteristics of the Study Population According to the Duration of Antiplatelet Therapy After Propensity Score Matching

Variable	DAPT< 6 mon or SAPT (N=206)	DAPT≥ 6 mon (n=170)	*P* value	SD	DAPT< 6 mon or SAPT (N=190)	DAPT≥ 6 mon (N=200)	*P* value	SD
Age (y)	72±10	68±11	<0.001	0.357	72±11	72±11	0.880	0.048
Male	151 (73.3)	134 (78.8)	0.261	0.138	139 (73.2)	127 (64)	0.048	0.039
Critical limb ischemia	92 (44.7)	54 (31.8)	0.014	-0.294	88 (46.3)	103 (51.8)	0.278	-0.104
Hypertension	284 (75.5)	159 (77.2)	0.484	-0.075	148 (77.9)	154 (77.4)	0.901	-0.020
Diabetes	106 (51.5)	91 (53.5)	0.767	0.036	101 (53.2)	110 (55.1)	0.699	-0.067
Dyslipidemia	10 (4.9)	21 (12.4)	0.015	0.270	10 (5.3)	10 (4.9)	0.852	-0.058
Congestive heart failure	30 (14.6)	20 (11.8)	0.520	-0.108	28 (14.7)	45 (22.7)	0.044	0.025
Chronic kidney disease	61 (29.6)	48 (28.2)	0.858	-0.072	59 (31.1)	64 (32.4)	0.773	0.055
Coronary artery disease	83 (40.3)	99 (58.2)	0.001	0.357	78 (41.1)	74 (36.9)	0.403	0.051
Stroke	43 (20.9)	28 (16.5)	0.340	-0.151	43 (22.6)	47 (24.0)	0.748	-0.042
Statin	162 (78.6)	155 (91.2)	0.001	0.367	149 (78.4)	147 (73.4)	0.249	0.118
RAAS-blocker	89 (43.2)	75 (44.1)	0.942	0.015	83 (43.7)	103 (51.6)	0.12	0.034
β-blocker	69 (33.5)	68 (40.0)	0.231	0.102	68 (35.8)	88 (44.3)	0.086	-0.069
Current smoker	66 (32.0)	63 (37.1)	0.362	0.125	58 (30.5)	59 (29.8)	0.884	0.000
Body mass index (kg/m^2)	22.7±3.8	23.0±4.4	0.468	-0.070	22.7±3.9	23.7±3.6	0.294	-0.044
Hemoglobin (g/dL)	11.7±2.1	12.5±2.1	<0.001	-0.399	11.7±2.0	11.6±2.3	<0.001	-0.075
Albumin (g/dL)	3.7±0.6	3.8±0.5	0.013	-0.271	3.7±0.6	3.7±0.6	0.027	-0.043
Low-density lipoprotein (mg/dL)	72±44	82±42	0.016	-0.240	71.2±42.9	75.4±41.9	0.016	-0.040
TASC Classification			0.223				0.498	
A	34 (16.6)	38 (22.4)			31 (16.3)	28 (14.3)		
B	55 (26.8)	45 (26.5)			50 (26.3)	42 (21.0)		
C	61 (29.8)	55 (32.4)			54 (28.4)	62 (31.2)		
D	55 (26.8)	32 (18.8)			55 (28.9)	67 (33.6)		
Below-knee lesion	78 (37.9)	42 (24.7)	0.009	-0.321	75 (39.5)	85 (42.5)	0.538	-0.504
Stent implantation	115 (55.8)	130 (76.5)	<0.001	0.465	106 (55.8)	111 (55.6)	0.971	0.109
Index procedure date (2015~)	108 (52.4)	96 (56.5)	0.433	0.061	101 (53.2)	125 (63.0)	0.048	0.033

Data are presented as mean ± standard deviation or numbers (percentages).

DAPT: dual antiplatelet-therapy; RAAS: renin-angiotensin-aldosterone system blocker; SAPT: single-antiplatelet therapy; SD: Standardized Difference; TASC: Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease classification

Table 2: Hazard Ratio of Clinical Events on the Basis of DAPT Duration After IPTW Matching and Propensity Score Matching

Variable	Unadjusted HR (95% CI)	*P* value	IPTW-Adjusted HR (95% CI)	*P* value	Propensity Score-Matched HR (95% CI)	*P* value
MACE	0.424 (0.254-0.708)	0.001	0.559 (0.351-0.888)	0.014	0.551 (0.297-0.986)	0.048
Death	0.338 (0.184-0.620)	0.001	0.523 (0.317-0.863)	0.011	0.495 (0.236-1.002)	0.053
Myocardial infarction	1.853 (0.338-10.514)	0.477	2.343 (0.411-12.32)	0.240	1.351 (0.226-8.098)	0.712
Stroke	0.450 (0.112-1.801)	0.259	0.996 (0.660-1.505)	0.986	0.535 (0.119-2.415)	0.416
MALE	1.033 (0.605-1.763)	0.905	1.054 (0.623-1.783)	0.846	0.859 (0.497-1.791)	0.944
Major amputation	0.650 (0.162-2.740)	0.561	1.807 (0.619-5.280)	0.279	0.616 (0.124-3.054)	0.553
Repeat revascularization	1.120 (0.622-1.993)	0.713	0.837 (0.455-1.542)	0.569	1.115 (0.597-2.084)	0.733
Moderate-to-severe bleeding	0.590 (0.214-1.627)	0.308	0.843 (0.350-2.032)	0.703	0.831 (0.222-3.102)	0.782
Severe bleeding	0.917 (0.129-6.519)	0.931	1.616 (0.291-8.963)	0.583	0.998 (0.229-4.575)	0.644

Values are represented as n (%).

CI: confidence interval; DAPT: dual-antiplatelet therapy; HR: hazard ratio; IPTW: inverse probability of treatment weighting; MACE: major adverse cardiovascular events; MALE: major adverse limb events; SAPT: single-antiplatelet therapy

Table 3: Baseline Characteristics on the Basis of the Duration of Dual-Antiplatelet Therapy

Variable	Total (N =376)	DAPT < 6 mon or SAPT (N=206)	DAPT ≥ 6 mon (N=170)	*P* value
Age (y)	70±11	72 ± 10	68 ± 11	< 0.001
Male	285 (75.8)	151 (73.3)	134 (78.8)	0.261
Body mass index (kg/m^2)	22.8±4.1	22.7±3.8	23±4.4	0.468
Current smoker	129 (34.3)	66 (32.0)	63 (37.1)	0.362
Hypertension	284 (75.5)	159 (77.2)	125 (73.5)	0.484
Diabetes mellitus	197 (52.4)	106 (51.5)	91 (53.5)	0.767
Dyslipidemia	31 (8.2)	10 (4.9)	21 (12.4)	0.015
Chronic kidney disease	109 (29.0)	61 (29.6)	48 (28.2)	0.858
Congestive heart failure	50 (13.3)	30 (14.6)	20 (11.8)	0.520
Coronary artery disease	182 (48.4)	83 (40.3)	99 (58.2)	0.001
Previous myocardial infarction	37 (9.8)	22 (10.7)	15 (8.8)	0.669
Previous stroke	71 (18.9)	43 (20.9)	28 (16.5)	0.340
Previous percutaneous transluminal angioplasty	25 (6.6)	11(5.3)	14 (8.2)	0.361
Medication				
Aspirin	322 (85.6)	152 (73.8)	170 (100.0)	0.001
Clopidogrel	275 (73.1)	105 (51.0)	170 (100.0)	0.001
Cilostazol	215 (57.2)	126 (61.2)	89 (52.4)	0.107
Statin	317 (84.3%)	162 (78.6)	155 (91.2)	0.001
Renin-angiotensin-aldosterone system blocker	164 (43.6)	89 (43.2)	75 (44.1)	0.942
Calcium channel blocker	149 (39.6)	83 (40.3)	66 (38.8)	0.854
β-blocker	137 (36.4)	69 (33.5)	68 (40.0)	0.231
Insulin	50 (13.3)	26 (12.6)	24 (14.1)	0.785
Hemoglobin (g/dL)	12.1±2.1	11.7± 2.1	12.5±2.1	<0.001
White blood cell (1000/uL)	8.8±3.5	9.0±3.9	8.5±2.8	0.103
Platelet (1000/uL)	235±85	236±90	234±77	0.877
Creatinine (mg/dL)	1.6±2.1	1.7±2.2	1.5±2.0	0.387
Total cholesterol (mg/dL)	148±43	146±41	151±46	0.232
Triglyceride (mg/dL)	144±103	134±105	155±100	0.061

Low-density lipoprotein (mg/dL)	76±43	72±44	82±42	0.016
High-density lipoprotein (mg/dL)	38±11	39±11	38±11	0.895
Aspartate aminotransferase (IU/L)	33±77	37±100	29±35	0.306
Alanine aminotransferase (IU/L)	22±34	22±30	22±39	0.864
Albumin (g/dL)	3.7±0.6	3.7±0.6	3.8±0.5	0.013
Follow-up duration (mon)	37±26	35±30	43±32	0.023

Data are presented as mean ± standard deviation or numbers (percentages).
DAPT: dual-antiplatelet therapy; SAPT: single-antiplatelet therapy

Table 4: Procedural Data on the Basis of the Duration of Dual-Antiplatelet Therapy

Variable	Total (N =376)	DAPT < 6 mon or SAPT (N=206)	DAPT ≥ 6 mon (n=170)	*P* value
Critical limb ischemia	144 (38.5)	92 (44.7)	54 (31.8)	0.014
Target Vessel				
Aortoiliac	149 (39.5)	74 (35.9)	75 (44.1)	0.131
Femoropopliteal	237 (63.0)	132 (64.1)	105 (61.8)	0.723
Below knee	120 (31.9)	78 (37.9)	42 (24.7)	0.009
Multilevel disease (target lesion)	119 (31.6)	73 (35.4)	46 (27.1)	0.104
TASC Classification				0.223
A	72 (19.2)	34 (16.6)	38 (22.4)	
B	100 (26.7)	55 (26.8)	45 (26.5)	
C	116 (30.9)	61 (29.8)	55 (32.4)	
D	87 (23.2)	55 (26.8)	32 (18.8)	
Type of Intervention				
Balloon	362 (96.3)	195 (94.7)	167 (98.2)	0.121
Stent	245 (65.2)	115 (55.8)	130 (76.5)	<0.001
Atherectomy	20 (5.3)	12 (5.8)	8 (4.7)	0.802
Hemodynamics				
Pre-ankle-brachial index	0.7/0.7	0.7/0.7	0.7/0.7	
Post-ankle-brachial index	0.9/0.9	0.9/0.9	0.9/0.9	

DAPT: dual-antiplatelet therapy; SAPT: single-antiplatelet therapy; TASC: Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease classification

Table 5: Incidence of Clinical Outcomes According to DAPT Duration

	DAPT< 6 mon or SAPT (N=206)			DAPT ≥ 6 mon (n=170)		
	Event	Person Year	Annual Incidence	Event	Person Year	Annual Incidence
MACE	49 (23.8)	566.84	0.086	21 (12.4)	628.73	0.033
Death	42 (20.4)	591.46	0.071	14 (8.2)	643.63	0.022
Myocardial infarction	2 (1.0)	582.23	0.003	4 (2.4)	631.64	0.006
Stroke	6 (2.9)	574.91	0.010	3 (1.8)	640.72	0.005
MALE	27 (13.1)	502.39	0.054	29 (17.1)	543.15	0.053
Repeat Revascularization	21 (10.2)	508.69	0.041	26 (15.3)	550.11	0.047
Major amputation	6 (2.9)	584.58	0.010	3 (1.8)	636.67	0.005
Moderate-to-severe bleeding	10 (4.9)	569.53	0.018	6 (3.5)	634.82	0.009
Severe bleeding	2 (1.0)	591.42	0.003	2 (1.2)	643.01	0.003

DAPT: dual-antiplatelet therapy; MACE: major adverse cardiovascular events; MALE: major adverse limb events; SAPT: single-antiplatelet therapy.

Table 6: Hazard Ratio of the Prolonged DAPT Group After Endovascular Revascularization With Cox Regression Analysis

Variable	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
MACE	0.424 (0.254-0.708)	0.001	0.541 (0.310-0.943) *	0.030
MALE	1.033 (0.605-1.763)	0.905	1.041 (0.601-1.806) †	0.885
Moderate-to-severe bleeding	0.590 (0.214-1.627)	0.308	0.560 (0.261-1.255) ‡	0.127

CI: confidence interval; DAPT: dual-antiplatelet therapy; HR: hazard ratio; MACE: major adverse cardiovascular events; MALE: major adverse limb events; RAAS: renin-angiotensin-aldosterone system blocker
* Age, congestive heart failure, chronic kidney disease, albumin, critical limb ischemia, and Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) were included in multivariate analysis.
† Below-knee lesion, hemoglobin, and index procedure period (2015~) were included in multivariate analysis.
‡ Age, hemoglobin, and RAAS were included in multivariate analysis.

Table 7: Baseline Characteristics of the Study Population According to the Duration of Antiplatelet Therapy After IPTW Matching

Variable	DAPT< 6 mon or SAPT (N=206)	DAPT ≥ 6 mon (n=170)	*P* value	SD	DAPT< 6 mon or SAPT (N=119)	DAPT ≥ 6 mon (N=119)	*P* value	SD
Age (y)	72±10	68±11	<0.001	0.357	69±11	69±12	0.876	0.021
Male	151 (73.3)	134 (78.8)	0.261	0.138	87 (73.1)	89 (74.8)	0.883	0.041
Critical limb ischemia	92 (44.7)	54 (31.8)	0.014	-0.294	44 (37.0)	43 (36.1)	1.0	-0.018
Hypertension	284 (75.5)	159 (77.2)	0.484	-0.075	85 (71.4)	88 (73.9)	0.771	0.057
Diabetes	106 (51.5)	91 (53.5)	0.767	0.036	60 (50.4)	59 (49.6)	1.0	-0.017
Dyslipidemia	10 (4.9)	21 (12.4)	0.015	0.270	9 (7.6)	9 (7.6)	1	0
Congestive heart failure	30 (14.6)	20 (11.8)	0.520	-0.108	14 (11.8)	17 (14.3)	0.700	0.078
Chronic kidney disease	61 (29.6)	48 (28.2)	0.858	-0.072	36 (30.3)	33 (27.7)	0.775	-0.056
Coronary artery disease	83 (40.3)	99 (58.2)	0.001	0.357	60 (50.4)	58 (48.7)	0.897	-0.034
Stroke	43 (20.9)	28 (16.5)	0.340	-0.151	18 (15.1)	24 (20.2)	0.395	0.136
Statin	162 (78.6)	155 (91.2)	0.001	0.367	102 (85.7)	105 (88.2)	0.700	0.089
RAAS-blocker	89 (43.2)	75 (44.1)	0.942	0.015	53 (44.5)	54 (45.4)	1.0	0.017
β-blocker	69 (33.5)	68 (40.0)	0.231	0.102	44 (37.0)	45 (37.8)	1.0	0.017
Current smoker	66 (32.0)	63 (37.1)	0.362	0.125	44 (37.0)	39 (32.8)	0.586	-0.087
Body mass index (kg/m^2)	22.7±3.8	23.0±4.4	0.468	-0.070	22.9±3.5	23.2±3.7	0.532	0.079
Hemoglobin (g/dL)	11.7±2.1	12.5±2.1	<0.001	-0.399	12.2±2.0	12.2±2.0	0.900	0.016
Albumin (g/dL)	3.7±0.6	3.8±0.5	0.013	-0.271	3.8±0.5	3.8±0.6	0.981	-0.003
Low-density lipoprotein (mg/dL)	72±44	82±42	0.016	-0.240	80±42.6	81.2±43.3	0.828	0.029
TASC Classification			0.223				0.881	
A	34 (16.6)	38 (22.4)			23 (19.3)	23(19.3)		0
B	55 (26.8)	45 (26.5)			30 (25.2)	32 (26.9)		0.038
C	61 (29.8)	55 (32.4)			38 (31.9)	41 (34.5)		0.054
D	55 (26.8)	32 (18.8)			28 (23.5)	23 (19.3)		-0.095
Below-knee lesion	78 (37.9)	42 (24.7)	0.009	-0.321	34 (28.6)	31 (26.1)	0.771	-0.059
Stent implantation	115 (55.8)	130 (76.5)	<0.001	0.465	83 (69.7)	84 (70.6)	1.0	0.019
Index procedure date (2015~)	108 (52.4)	96 (56.5)	0.433	0.061	70 (58.8)	65 (54.6)	0.601	-0.085

Data are presented as mean ± standard deviation or numbers (percentages).

DAPT: dual-antiplatelet therapy; IPTW: inverse probability of treatment weighting; RAAS: renin-angiotensin-aldosterone system blocker; SAPT: single-antiplatelet therapy; SD: standardized difference; TASC: Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease classification

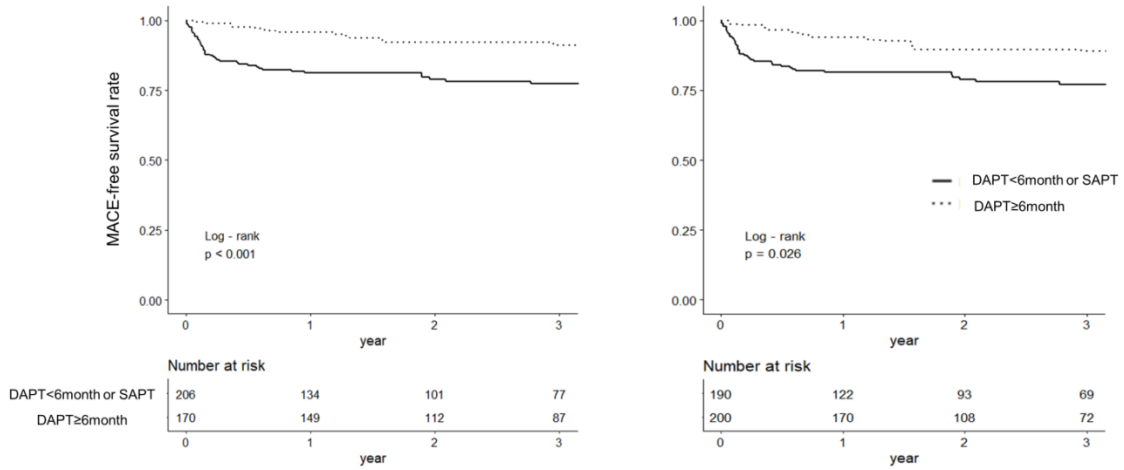

Figure 1: The images illustrate the Kaplan–Meier curve for the MACE-free survival rate before (1A) and after IPTW matching (1B) according to DAPT duration.
MACE: major cardiovascular event; IPTW: inverse probability treatment weighting

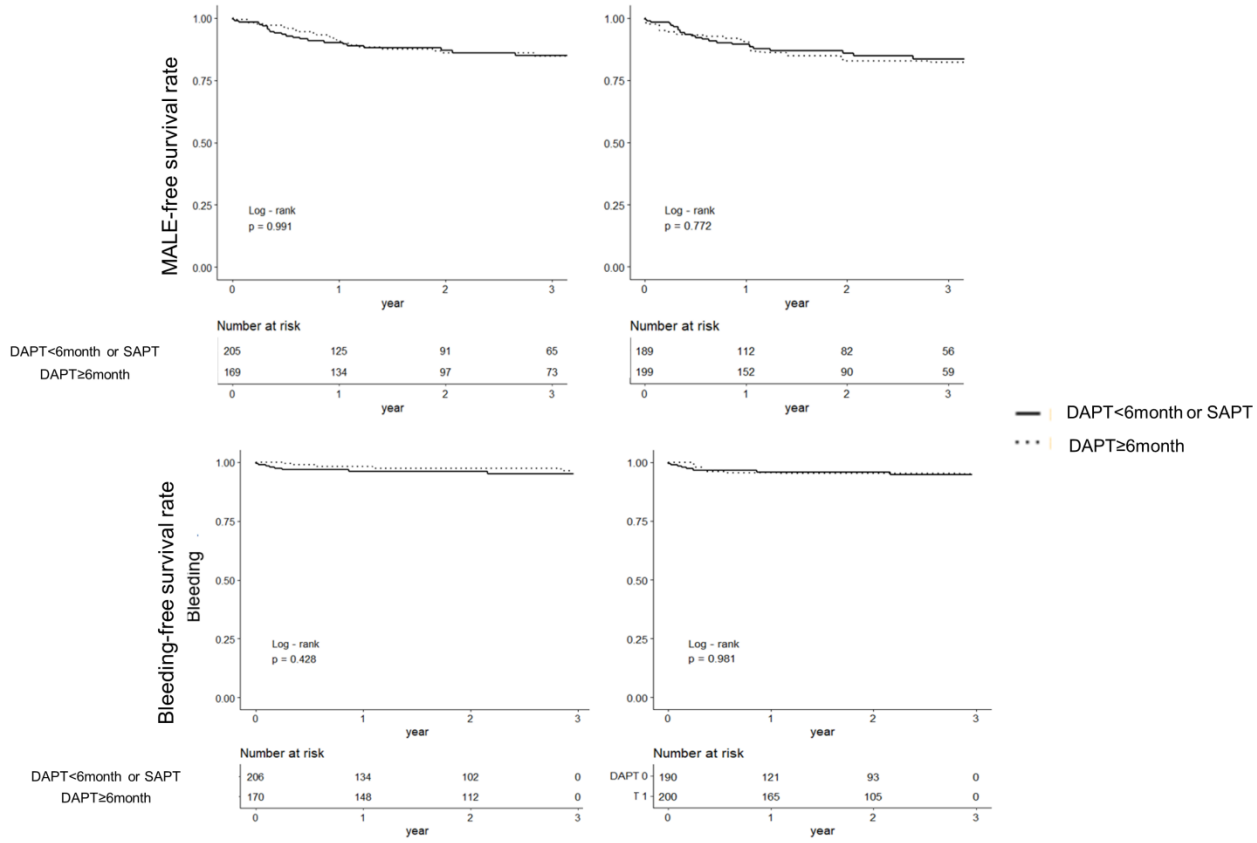

Figure 2: The images present the Kaplan–Meier curve for the MALE-free survival rate and the bleeding-free survival rate before and after IPTW matching according to DAPT duration.
2A. Kaplan–Meier curve for the MALE-free survival rate before IPTW matching
2B. Kaplan–Meier curve for the MALE-free survival rate after IPTW matching
2C. Kaplan–Meier curve for the bleeding-free survival rate before IPTW matching
2D. Kaplan–Meier curve for the bleeding-free survival rate after IPTW matching

DAPT: dual-antiplatelet therapy; IPTW: inverse probability treatment weighting; MACE: major cardiovascular event; MALE: major adverse limb event; SAPT: single-antiplatelet therapy

DISCUSSION

The principal findings of our analysis are as follows:

1) In real-world practice, there was significant variability in the duration of antiplatelet therapy after endovascular revascularization for LEAD.
2) DAPT ≥ 6 months was associated with significantly lower rates of MACE than DAPT < 6 months or SAPT, without evidence of increased bleeding events.
3) DAPT ≥ 6 months was an independent predictor of a reduced risk for MACE.

In the 2016 AHA/ACC lower extremity PAD guideline, aspirin alone or clopidogrel alone was recommended in patients with symptomatic PAD. Nevertheless, the effectiveness of DAPT in reducing the risk of cardiovascular ischemic events in patients with symptomatic PAD has not been well established. There are limited data suggesting that DAPT may be reasonable to reduce the risk of limb-related events after lower extremity revascularization among patients with symptomatic PAD. [7] According to the 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, which were developed in collaboration with the European Society for Vascular Surgery, SAPT is indicated for patients with symptomatic LEAD and DAPT may be considered in LEAD patients with CAD. DAPT for at least 1 month after percutaneous revascularization should be considered among patients with LEAD. [6] The post hoc analysis of the CHARISMA trial [15] demonstrated that among patients with PAD, the primary endpoints, which were MI, stroke of any cause, and death from cardiovascular causes, including hemorrhage, occurred less frequently in the clopidogrel plus aspirin group than those in the placebo plus aspirin group (HR, 0.85; *P* = 0.18). Among these patients, the dual-antiplatelet arm had lower rates of MI and hospitalization for ischemic events than the aspirin-alone arm (HR, 0.63; *P* = 0.029) at the cost of an increase in minor bleeding. As a randomized trial, the MIRROR study [16] demonstrated that DAPT reduced peri-interventional platelet activation more than aspirin alone and improved functional outcomes without causing higher bleeding complications in patients with PAD treated with endovascular therapy.

Soden et al [9] examined DAPT at the time of discharge and found that in comparison with aspirin alone, DAPT was associated with prolonged survival for patients with CLI undergoing lower extremity revascularization. However, they did not evaluate bleeding complications. Cho et al [10] evaluated the optimal duration for antiplatelet therapy after endovascular revascularization in patients with lower extremity PAD. In their study, MACE occurred less frequently in the DAPT ≥ 6-month group than in the DAPT < 6-month or SAPT group (HR, 0.44; *P* < 0.001), and MALE occurred less frequently in the DAPT ≥ 6-month group than in the DAPT < 6-month or SAPT group (HR, 0.42; *P* < 0.001) without increasing major bleeding events. Nonetheless, procedures using atherectomy devices were not included in their study.

In this study, the DAPT ≥ 6-month group showed less frequent MACE than the DAPT < 6-month or SAPT group without increasing the risk of bleeding in the IPTW-matched and PSM analysis; however, the incidence of MALE showed no significant difference. Patients with PAD who underwent endovascular revascularization procedures were patients with advanced atherosclerosis,

which is more likely to result in cardiovascular events. In line with this, our study showed that approximately 66% of patients had either previous CAD or stroke, and 29% of patients had chronic kidney disease. Thus, a strategy to reduce additional CVD events is important in a state wherein the proportion of patients with underlying CVD is high, as in our study. The 2 important drugs are statins and antiplatelet agents. [17] Specifically, antiplatelet therapy is typically recommended for the secondary prevention of CVD.

Moreover, during the endovascular revascularization procedure, the blood vessels are damaged by the wire, balloon angioplasty, stent deployment, and atherectomy device. This endothelial damage promotes the adhesion of platelets, platelet activation, and increased expression of adhesion molecules, resulting in the aggravation of atherosclerosis and ischemic events. Therefore, antiplatelet therapy is much more important for patients who have undergone endovascular procedures than those who have not. Prolonged use of dual-antiplatelet agents could be more effective in controlling platelet activation than the short-term use of DAPT or SAPT.

Therefore, the low incidence of MACE observed in the prolonged DAPT group in this observational study may be partially explained by the high incidence of other CVD events in patients with PAD and the increase in intravascular thrombogenicity before and after the procedure. No significant difference was noted in moderate-to-severe bleeding between the 2 groups in this study. A previous study also reported that no significant difference was observed between the 2 groups in the case of major bleeding. [10] However, in this study, the total number of patients may have been insufficient to confirm the difference in bleeding events, and the baseline characteristics showed that the prolonged DAPT group was younger and had fewer risk factors, increasing the risk of bleeding, such as hypertension and stroke. Therefore, it is believed that these differences may have affected the results of the bleeding event.

The use of prolonged DAPT after percutaneous revascularization remains controversial in the setting of CAD. According to a recent meta-analysis from 6 randomized trials, Valgimigli et al [18] reported that P2Y12 inhibitor monotherapy was associated with lower rates of major bleeding than DAPT with a similar risk of fatal and ischemic events. P2Y12 inhibitor monotherapy may be particularly beneficial among female patients with lower cardiovascular mortality. According to Sprito et al, [19] female sex is an independent predictor for access-site bleeding, especially from the femoral artery after percutaneous coronary intervention. Although the difference in bleeding events between the male and female groups was not observed in our study, P2Y12 inhibitor monotherapy may be considered for female sex after endovascular revascularization via the femoral artery approach.

In another study using real-world data, Cesaro et al [20] showed that a lower dose of ticagrelor for prolonged DAPT could reduce bleeding risk in patients with high ischemic risk and previous MI. In our study, clopidogrel was the only P2Y12 inhibitor. Newer P2Y12 inhibitors with a low-dose regimen could also be considered an option for patients with high bleeding risk. However, these need further studies.

Thus, for patients with LEAD after endovascular revascularization, prolonged DAPT beyond 6 months may be reasonable to possibly prevent adverse cardiovascular events. Further prospective studies are needed to show whether the use of DAPT for periods longer than 6 months improves clinical outcomes.

Study Limitations

This study had several limitations. Firstly, we reported the outcomes from a single center. Therefore, our findings are not generalizable. Secondly, this was a retrospective, non-randomized study, and the study design may have introduced selection biases and unmeasured data. However, we reduced this bias by performing multivariate Cox and IPTW analyses. Thirdly, in our study, the use of medication was at the physicians' discretion. Fourthly, due to the limited number of patients and clinical events, the present trial was underpowered to detect a significant difference in terms of bleeding outcomes. Fifthly, the 3-year follow-up period was relatively short. Thus, it is difficult to generalize conclusions or to reveal casual relationships. Lastly, the outcomes were clinical events or revascularization, since angiography and CT were not performed routinely. Hence, there was a high possibility that the vascular outcome was underestimated.

CONCLUSIONS

DAPT ≥ 6 months after endovascular revascularization in patients with LEAD was associated with a lower incidence of MACE.

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※ MSIT: Ministry of Science and Information and Communications Technology

Conflict of Interest

None

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