Dual-Antiplatelet Therapy for More Than Six Months After Endovascular Revascularization in Patients With Lower-Extremity Artery Disease

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Abstract

Background: The duration of antiplatelet therapy after endovascular revascularization in patients with lower-extremity artery disease (LEAD) has not been well-established. This study aimed to investigate the optimal strategy for antiplatelet therapy after successful endovascular revascularization in patients with LEAD.

Methods: From April 2009 to June 2019, 376 patients with LEAD underwent successful endovascular revascularization. After the procedure, the patients received mono-antiplatelet therapy (MAPT) or dual-antiplatelet therapy (DAPT) of various durations and were classified into 2 groups (MAPT or DAPT < 6 months vs. DAPT $\geq$ 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 $\geq$ 6 months group than the MAPT or DAPT < 6 months group (12.4% vs. 23.8%; hazard ratio: 0.62; 95% confidence interval: 0.40 to 0.97; $p = 0.038$) after inverse probability-weighted adjustment and propensity-score matching. The incidence of MALE showed no significant intergroup difference (17.1% vs. 13.1%; hazard ratio: 0.94; 95% confidence interval: 0.56 to 1.59; $p = 0.822$). The incidence of moderate-to-severe GUSTO bleeding also showed no significant intergroup difference (3.5% vs. 4.9%; hazard ratio: 0.59; 95% confidence interval: 0.21 to 1.63; $p = 0.308$).

Conclusions: For patients with LEAD, DAPT for ≥ 6 months after endovascular revascularization was associated with a lower incidence of MACE without increasing the risk of bleeding events.

Background

Peripheral artery disease (PAD) is one of the advanced forms of atherosclerosis, and lower-extremity artery disease (LEAD), which is a type of PAD, can present with intermittent claudication to critical limb ischemia (CLI).^(1–3) It is highly likely to be accompanied by coronary artery disease and carotid artery disease, and can result in major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke, and limb events such as amputation and repeat revascularization.^(3–5) Among patients with LEAD, those undergoing endovascular revascularization show more advanced disease, and antiplatelet agent administration is the mainstay of treatment after the procedure.^(6, 7) Dual-antiplatelet therapy may be reasonable to reduce the risk of MACE and major adverse limb events (MALE) after lower-extremity revascularization in patients with symptomatic LEAD.⁽⁸⁾ Although recent guidelines recommend one-month dual-antiplatelet therapy after lower-extremity interventions, data specifying the appropriate period beyond the one-month treatment are insufficient.^(9, 10) In comparison with the available information regarding antiplatelet therapy after coronary artery interventions, data for antiplatelet treatment after lower-extremity artery endovascular revascularization, including the choice between mono-antiplatelet therapy and dual-antiplatelet therapy and the duration of antiplatelet

treatment, are insufficient.(2, 11) Thus, we sought to determine an appropriate period of dual-antiplatelet therapy after endovascular revascularization for patients with LEAD. We also investigated the clinical outcomes, namely, the incidence of MACE and MALE and 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. Eighty-five 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). In total, 376 patients with symptomatic LEAD (claudication or CLI) were included in the study. The study protocol was approved by the institutional review board at the Sanggye Paik Hospital (2019-10-010). The study was carried out according to the Principles of the Declaration of Helsinki 1975 and its later amendments.

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, or severe claudication, respectively), while CLI was classified into categories 4–6 (ischemic rest pain, minor tissue loss, or 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.

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 II: aortoiliac and femoropopliteal levels, TASC I: infrapopliteal level),(12) number of diseased vessels, intervention type (balloon angioplasty, atherectomy, or stent insertion), and pre- and post-intervention ankle brachial index (ABI). Multilevel disease was defined by the presence of significantly obstructed lesions at ≥1 level in the same limb. Follow-up examinations, which included a physical examination, were conducted at two weeks postoperatively and then at intervals of 1–3 months.

Clinical outcomes

The primary end points were the incidence of MACE (major adverse cardiovascular events: composite occurrence of all-cause death, myocardial infarction, and stroke) and MALE (major adverse limb events; composite occurrence of unplanned repeat revascularization and major amputation).(13) 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. 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.(14) All events were diagnosed by experienced attending physicians, and the patients were reviewed by three cardiologists.

Statistical analysis

The chi-square test or Fisher's exact test was used to compare categorical variables, which were reported as numbers (percentages). Student's 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 used 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 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 antiplatelet groups, and to reduce the effect of selection bias and potential confounding between the two groups, we used inverse probability treatment weighting (IPTW) using propensity scores (PSs) on the basis of the demographic, laboratory, and treatment characteristics of patients.(15) The following 17 variables were commonly used as matching variables for IPTW: age, sex, critical limb ischemia, hypertension, dyslipidemia, heart failure, chronic kidney disease, coronary artery disease, stroke, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta blocker, insulin therapy, smoking status, body mass index, hemoglobin level, and serum albumin and low-density lipoprotein levels. To measure the balancing, we calculated the standardized bias for each measured covariate for the weighted samples. 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.

Results

Baseline characteristics

Patients were followed up for a mean duration of 40 months. Among the 376 patients, 206 received DAPT < 6 months or MAPT and 170 received DAPT ≥ 6 months. The baseline clinical characteristics of the study population are shown in Table 1. The two groups showed no significant differences in sex, body mass index, smoking history, and prevalence of hypertension, diabetes mellitus, chronic kidney disease, congestive heart failure, coronary artery disease, previous myocardial infarction, previous stroke, and previous percutaneous transluminal angioplasty. Patients in the DAPT ≥ 6 months group were younger, showed 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.

Table 1
Baseline characteristics on the basis of duration of dual antiplatelet therapy

Variables	Total (N = 376)	DAPT < 6month or MAPT (N = 206)	DAPT ≥ 6month (N = 170)	p value
Age (years)	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
Beta blocker	137 (36.4)	69 (33.5)	68 (40.0)	0.231

Data are presented as mean ± standard deviation or number (percentage). DAPT = dual antiplatelet agent; MAPT = mono antiplatelet agent therapy.

Variables	Total (N = 376)	DAPT < 6month or MAPT (N = 206)	DAPT ≥ 6month (N = 170)	p value
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 (1,000/uL)	8.8 ± 3.5	9.0 ± 3.9	8.5 ± 2.8	0.103
Platelet (1,000/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
Data are presented as mean ± standard deviation or number (percentage). DAPT = dual antiplatelet agent; MAPT = mono antiplatelet agent therapy.				

The two groups showed no significant differences in the incidences of multilevel disease and TASC classification, as described in Table 2. However, the proportion of patients with critical limb ischemia was higher in the DAPT < 6 months or MAPT group than in the DAPT ≥ 6 months group. Moreover, targeting for below-the-knee lesions was more frequent in the DAPT < 6 months or MAPT group. Stent insertion was performed more frequently in the DAPT ≥ 6 months group. The frequency of atherectomy-device usage during the procedure was similar in both groups (DAPT < 6 months or MAPT group: 5.8%, DAPT ≥ 6 months group: 4.7%; P = 0.802). The ABI measured before and after the procedure showed no significant difference between the two groups. All baseline variables after IPTW adjustment and propensity-score matching were well-balanced.

Table 2
Procedural data on the basis of duration of dual antiplatelet therapy

Variables	Total (N = 376)	DAPT < 6month or MAPT (N = 206)	DAPT ≥ 6month (n = 170)	p value
Critical limb ischemia	144 (38.5)	92 (44.7)	54 (31.8)	0.014
Target vessel				
Aorto-iliac	149 (39.5)	74 (35.9)	75 (44.1)	0.131
Femoro-popliteal	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 agent; MAPT = mono antiplatelet agent therapy; TASC = Trans Atlantic Inter Society Consensus for the Management of Peripheral Arterial Disease classification.				

Clinical Outcomes

Clinical outcomes in the DAPT < 6 months or MAPT group and the DAPT ≥ 6 months group are shown in Table 3. The MACE-related death rate was lower in the DAPT ≥ 6 months group (12.4% vs. 23.8%; HR: 0.42; 95% CI: 0.25 to 0.71; $p < 0.001$). The incidence of all-cause death was also lower in the DAPT ≥ 6 months group (8.2% vs. 20.4%; HR: 0.39; 95% CI: 0.18 to 0.62; $p < 0.001$). However, the incidence of myocardial infarction (MI) (2.4% vs. 1.0%; HR: 1.85; 95% CI: 0.34 to 10.51; $p = 0.477$) and stroke (1.8% vs. 2.9%; HR: 0.45; 95% CI: 0.11 to 1.80; $p = 0.259$) did not differ significantly between the two groups. The clinical benefit of DAPT ≥ 6 months was also consistent after IPTW adjustment and propensity-score matching. After IPTW adjustment, MACE occurred less frequently in the DAPT > 6 months group than in the DAPT < 6 months or MAPT group (HR: 0.62; 95% CI: 0.40 to 0.97; $p = 0.038$). All-cause death also occurred less frequently in the DAPT ≥ 6 months group (HR: 0.48; 95% CI: 0.29 to 0.81; $p < 0.0062$). The MALE rate was similar between the two groups (HR: 1.03; 95% CI: 0.61 to 1.76; $p = 0.905$), and propensity-score matching also showed no significant difference between the two groups (HR: 0.94; 95% CI: 0.56 to 1.59; $p = 0.822$). In the assessment of bleeding events, moderate-to-severe GUSTO bleeding showed no significant difference between the two groups (3.5% vs. 4.9%; HR: 0.59; 95% CI: 0.21 to 1.62; $p = 0.308$) and severe GUSTO bleeding also showed no difference between the two groups (1.2% vs. 1.0%; HR: 0.92; 95% CI: 0.13 to 6.52; $p = 0.931$) (Table 4).

Table 3
Clinical outcomes on the basis of DAPT duration

Variables	DAPT < 6month or MAPT (206)	DAPT > 6month (170)	Unadjusted HR (95% CI)	p value	IPTW adjusted HR (95% CI)	p value
MACE	49 (23.8)	21 (12.4)	0.424 (0.254– 0.708)	0.001	0.622 (0.397– 0.974)	0.038
Death	42 (20.4)	14 (8.2)	0.338 (0.184– 0.620)	0.001	0.483 (0.286– 0.813)	0.006
Myocardial infarction	2 (1.0)	4 (2.4)	1.853 (0.338– 10.514)	0.477	4.718 (0.65- 41.218)	0.161
Stroke	6 (2.9)	3 (1.8)	0.450 (0.112– 1.801)	0.259	0.908 (0.298– 2.766)	0.865
MALE	27 (13.1)	29 (17.1)	1.033 (0.605– 1.763)	0.905	0.942 (0.557– 1.592)	0.822

Values are represented as n (%). CI = confidence interval; DAPT = dual antiplatelet agent; HR = hazard ratio; IPTW = inverse probability of treatment weighting; MACE = major adverse cardiovascular events; MALE = major adverse limb events; MAPT = mono antiplatelet agent therapy.

Table 4
Safety endpoints (bleeding outcomes)

Variables	DAPT < 6month or MAPT (N = 206)	DAPT > 6month (n = 170)	HR (95% CI)	p value
Moderate bleeding	10 (4.9%)	6 (3.5%)	0.590 (0.214–1.627)	0.308
Severe bleeding	2 (1.0%)	2 (1.2%)	0.917(0.129–6.519)	0.931
CI = confidence interval; DAPT = dual antiplatelet agent, HR = Hazard ratio, MAPT = mono antiplatelet agent therapy.				

Predictors Of Mace And Male

The adverse clinical outcomes for the entire population predicted by univariate and multivariate Cox proportional survival analysis are shown in Table 5. DAPT $\geq$ 6 months was an independent predictor of a reduced risk for MACE (HR: 0.57; 95% CI: 0.33 to 0.98; $p < 0.042$), but it did not show statistical significance for the incidence of MALE (HR 1.16; 95% CI: 0.63 to 2.13; $p < 0.631$). The benefit of DAPT $\geq$ 6 months for MACE was consistent across multiple subgroups. Prescription of a renin-angiotensin-aldosterone system (RAAS)-blocker (HR: 0.57; 95% CI: 0.34 to 0.95; $p < 0.032$) was also identified as an independent predictor of a reduced risk for MACE, and prescription of statins was an independent predictor of reduced risk for both MACE (HR: 0.43; 95% CI: 0.26 to 0.72; $p < 0.001$) and MALE (HR: 0.46; 95% CI: 0.23 to 0.92; $p = 0.028$). Additionally, older age (HR: 1.05; 95% CI: 1.02 to 1.07; $p < 0.001$), heart failure (HR: 3.08; 95% CI: 1.81 to 5.25; $p < 0.001$), chronic kidney disease (HR: 2.57; 95% CI: 1.56 to 4.22; $p < 0.001$), and critical limb ischemia (HR: 1.81; 95% CI: 1.09 to 3.00; $p < 0.001$) were identified as predictors of MACE.

Table 5
Predictors of MACE and MALE after endovascular revascularization

	Univariate Analysis HR (95% CI)	p value	Multivariate analysis HR (95% CI)	p value
MACE				
Age (years)	1.067 (1.042–1.093)	< 0.001	1.045 (1.020–1.070)	< 0.001
Male	0.837 (0.489–1.434)	0.518		
Hypertension	2.092 (1.071–4.087)	0.031	1.491 (0.738–3.012)	0.265
Diabetes mellitus	0.883 (0.552–1.414)	0.605		
Heart failure	4.015 (2.415–6.675)	< 0.001	3.078 (1.806–5.247)	< 0.001
Chronic kidney disease	3.983 (2.468–6.341)	< 0.001	2.565 (1.558–4.223)	< 0.001
Previous stroke	0.954 (0.511–1.782)	0.882		
Previous myocardial infarction	1.725 (0.881–3.377)	0.112		
DAPT ≥ 6month	0.424(0.254–0.708)	0.001	0.568 (0.329–0.981)	0.042
Statin	0.325(0.197–0.536)	< 0.001	0.430 (0.256–0.723)	0.001
RAAS-blocker	0.554 (0.336–0.914)	0.021	0.568 (0.338–0.954)	0.032
Critical limb ischemia	2.758 (1.700-4.473)	< 0.001	1.807 (1.087–3.004)	0.022
MALE				
Age (years)	0.989 (0.964–1.015)	0.397	1.006 (0.981–1.033)	0.624
Male	0.934 (0.473–1.844)	0.844		
Hypertension	0.926 (0.478–1.793)	0.820	1.001 (0.501–1.997)	0.998
Diabetes mellitus	1.632 (0.893–2.984)	0.111		
Heart failure	0.048 (0.001-124.025)	0.560	0.424 (0.101–1.776)	0.241
Chronic kidney disease	0.835 (0.413–1.688)	0.616	0.808 (0.387–1.684)	0.569

CI = confidence interval; DAPT = dual antiplatelet agent; HR = hazard ratio; MACE = major adverse cardiovascular events; MALE = major adverse limb events; MAPT = mono antiplatelet agent therapy; RAAS = Renin angiotensin aldosterone system; TASC = Trans Atlantic Inter Society Consensus for the Management of Peripheral Arterial Disease classification.

	Univariate Analysis HR (95% CI)	p value	Multivariate analysis HR (95% CI)	p value
Previous stroke	1.862 (0.977–3.549)	0.059		
Previous myocardial infarction	1.256 (0.496–3.183)	0.631		
DAPT > 6month	1.046 (0.583–1.878)	0.879	1.160 (0.632–2.129)	0.631
Statin	0.427 (0.216–0.842)	0.014	0.458 (0.228–0.919)	0.028
RAAS-blocker	1.023 (0.569–1.838)	0.940	0.893 (0.481–1.657)	0.720
Critical limb ischemia	1.563 (0.868–2.815)	0.137	1.676 (0.913–3.075)	0.096
TASC C or D lesion	1.946 (1.102–3.438)	0.022	1.805 (0.941–3.463)	0.076
CI = confidence interval; DAPT = dual antiplatelet agent; HR = hazard ratio; MACE = major adverse cardiovascular events; MALE = major adverse limb events; MAPT = mono antiplatelet agent therapy; RAAS = Renin angiotensin aldosterone system; TASC = Trans Atlantic Inter Society Consensus for the Management of Peripheral Arterial Disease classification.				

Discussion

The main 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 MAPT, without evidence of increased bleeding events; and 3) DAPT ≥ 6 months was an independent predictor of a reduced risk for MACE, with its benefit appearing consistently across multiple subgroups.

In the 2016 AHA/ACC lower-extremity PAD guideline, aspirin alone or clopidogrel alone was recommended in patients with symptomatic PAD. However, 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.(9) 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 (ESVC), single antiplatelet agent therapy is indicated for patients with symptomatic LEAD and dual-antiplatelet agent therapy may be considered in LEAD patients with coronary artery disease. Dual-antiplatelet therapy for at least 1 month after percutaneous revascularization should be considered among patients with LEAD.(8) The post-hoc analysis of CHARISMA trial(16) demonstrated that among patients with PAD, the primary endpoints, which were MI, stroke of any cause, or death from cardiovascular causes including hemorrhage, occurred less frequently in the clopidogrel plus aspirin group than in the placebo plus aspirin group (HR, 0.85; P = 0.18). Among these patients, the rate of MI and the rate of hospitalization for ischemic events were lower in the dual-antiplatelet arm 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(17) 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.(18) studied DAPT at 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 but not for those showing claudication. However, they did not evaluate bleeding complications. Cho et al.(19) evaluated the optimal duration for antiplatelet therapy after endovascular revascularization in patients with lower-extremity peripheral artery disease. In their study, MACE occurred less frequently in the DAPT $\geq$ 6 months group than the DAPT < 6 months or MAPT group (hazard ratio: 0.44; $p < 0.001$), and MALE also occurred less frequently in the DAPT $\geq$ 6 months group than in the DAPT < 6 months or MAPT group (hazard ratio: 0.42; $p < 0.001$) without increasing major bleeding events. However, procedures using atherectomy devices were not included in their study.

According to our study, the DAPT $\geq$ 6 months group showed less frequent major adverse cardiovascular events than the DAPT < 6 months or MAPT group without increasing the risk of bleeding in IPTW matched analysis, although the incidence of MALE showed no significant difference. Patients with PAD who underwent the endovascular revascularization procedure were patients with advanced atherosclerosis, which is more likely to result in cardiovascular events. Moreover, during the endovascular revascularization procedure, the blood vessels are damaged by the wire, balloon angioplasty, stent deployment, and atherectomy device. This endothelial damage promoted the adhesion of platelets, platelet activation, and increased expression of adhesion molecules, results in the aggravation of atherosclerosis and ischemic events. Thus, antiplatelet therapy is much more important for patients who have undergone endovascular procedures than for those who have not. Prolonged use of dual antiplatelet agents could be more effective in controlling platelet activation than short-term use of dual antiplatelet agents and mono-antiplatelet therapy.

Soden et al.(18) showed that dual antiplatelet therapy after lower-extremity revascularization is associated with prolonged survival in patients with CLI. They suggested that DAPT and discharge on statin are favorable predictors for long-term mortality and reported the following unfavorable predictors for long-term mortality: age, white ethnicity, current smoker, diabetes, coronary artery disease, congestive heart failure, renal dysfunction, hemodialysis, prior major amputation, urgent procedure, and perioperative anticoagulation. Gaurav et al.(15) reported that statin use in patients receiving PAD with interventions was associated with improved limb salvage and survival.

Armstrong et al.(20) investigated the effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for patients with CLI who underwent diagnostic angiography or endovascular intervention. After a 3-year follow up, patients prescribed ACEIs or ARBs had lower rates of MACE (HR: 0.76, 95% CI 0.58–0.99, $p = 0.04$) and overall mortality (HR: 0.71, 95% CI 0.53–0.95, $p = 0.02$), but the medications had no effect on limb-related outcomes.

In our study, DAPT $\geq$ 6 months was an independent predictor of reduced MACE in multivariate Cox analysis. Its benefit was consistent across multiple subgroups. Moreover, age, heart failure, chronic kidney disease, statin administration, use of an RAAS blocker, and CLI were predictors of MACE. The use of statins is a predictor of MALE. Thus, for patients with LEAD after endovascular revascularization, prolonged DAPT beyond 6 months may be reasonable to possibly prevent adverse cardiovascular events, and statin use may be considered to prevent limb 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. First, we reported the outcomes from a single center. Therefore, our findings are not generalizable. In addition, 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. Third, in our study, the use of medication was at the physicians' discretion. Last, the outcomes were clinical events or revascularization, since angiography and CT were not performed routinely. Thus, there was a high possibility that the vascular outcome was overestimated.

Conclusions

DAPT $\geq$ 6 months after endovascular revascularization in patients with LEAD was associated with decreased MACE without an increase in major and moderate bleeding events. A prospective randomized trial is needed to confirm these findings.

List Of Abbreviations

CLI, critical limb ischemia

DAPT, dual-antiplatelet therapy

GUSTO, Global Use of Strategies to Open Occluded Arteries

IPTW, inverse probability treatment weighting

LEAD, lower-extremity artery disease

MACE, major adverse cardiovascular events

MALE, major adverse limb events

MAPT, mono-antiplatelet therapy

PAD, Peripheral artery disease

PS, propensity scores

TASC, Trans-Atlantic Inter Society Consensus for the Management of Peripheral Arterial Disease classification

Declarations

Authors' Contributions

JK Seo and BG Kim have drafted and revised the manuscript

GS Kim and YS Byun contributed to interpretation and conception of study

MN Jin and HY Lee contributed to acquisition and analysis of data

BO Kim designed this study

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※ MSIT: Ministry of Science and Information and communications Technology

Availability of data and materials

The data used and analyzed in this study are available from the corresponding author on reasonable request

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Ethics approval and consent to participate

The study protocol was approved by the institutional review board at the Sanggye Paik Hospital (2019-10-010). Written informed consent was obtained from all participants.

Consent for publication

All coauthors have seen and agree with the contents of the manuscript. Neither the entire paper nor any part of its content has been under simultaneous consideration elsewhere and has not been previously published in similar form

Conflicts of interest

The authors declare that they have no competing interests.

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