



















ORIGINAL RESEARCH

Effect of Cilostazol on Patients With Diabetes Who Underwent Endovascular Treatment for Peripheral Artery Disease

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BACKGROUND: No large-scale study has compared the clinical impact of triple antiplatelet therapy (TAPT: aspirin, clopidogrel, and cilostazol) and dual antiplatelet therapy (DAPT) on adverse limb events in patients with diabetes after endovascular therapy (EVT) for peripheral artery disease. Thus, we investigate the effect of cilostazol added to a DAPT on the clinical outcomes after EVT in patients with diabetes using a nationwide, multicenter, real-world registry.

METHODS AND RESULTS: A total of 990 patients with diabetes who underwent EVT were enrolled from the retrospective cohorts of a Korean multicenter EVT registry and were divided according to the antiplatelet regimen (TAPT [n=350; 35.4%] versus DAPT [n=640; 64.6%]). After propensity score matching based on clinical characteristics, a total of 350 pairs were compared for clinical outcomes. The primary end points were major adverse limb events, a composite of major amputation, minor amputation, and reintervention. For the matched study groups, the lesion length was 125.4±102.0 mm, and severe calcification was observed in 47.4%. The technical success rate (96.9% versus 94.0%; $P=0.102$) and the complication rate (6.9% versus 6.6%; $P>0.999$) were similar between the TAPT and DAPT groups. At 2-year follow-up, the incidence of major adverse limb events (16.6% versus 19.4%; $P=0.260$) did not differ between the 2 groups. However, the TAPT group showed less minor amputation than the DAPT group (2.0% versus 6.3%; $P=0.004$). In multivariate analysis, TAPT was an independent predictor of minor amputation (adjusted hazard ratio, 0.354 [95% CI, 0.158–0.794]; $P=0.012$).

CONCLUSIONS: In patients with diabetes undergoing EVT for peripheral artery disease, TAPT did not decrease the incidence of major adverse limb events but may be associated with a decreased risk of minor amputation.

Key Words: cilostazol ■ critical limb ischemia ■ diabetes ■ peripheral artery disease ■ triple antiplatelet therapy

D diabetes is a major predictor of worse clinical outcomes of peripheral artery disease (PAD).¹ Compared with patients without diabetes, the amputation rate is higher in patients with diabetes because of the common involvement of the infrapopliteal arteries.^{2,3} In addition, despite the advanced endovascular

intervention era, patients with diabetes have challenges in terms of improving the clinical outcomes attributable to complex baseline characteristics including peripheral neuropathy, microvasculature insufficiency, and high prevalence of chronic kidney disease and critical limb ischemia.^{2,3}

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CLINICAL PERSPECTIVE

What Is New?

- Triple antiplatelet therapy, consisting of aspirin, clopidogrel, and cilostazol, was associated with a reduced risk of minor amputation in patients with diabetes who underwent endovascular therapy compared with dual antiplatelet therapy consisting of aspirin and clopidogrel.

What Are the Clinical Implications?

- Although various studies have reported the beneficial effects of cilostazol on stroke, coronary stent restenosis, and ischemic vascular events, particularly in patients with diabetes, there is limited evidence on the best antithrombotic therapy including cilostazol in patients who underwent endovascular treatment for peripheral artery disease, particularly in diabetes.
- The present study suggests that triple antiplatelet therapy including cilostazol would reduce the risk of minor amputation in patients with diabetes who underwent endovascular treatment for peripheral artery disease.

Nonstandard Abbreviations and Acronyms

CLI	critical limb ischemia
DAPT	dual antiplatelet therapy
EVT	endovascular therapy
K-VIS ELLA	The Korean Vascular Intervention Society Endovascular Therapy in the Lower Limb Artery Diseases
MALEs	major adverse limb events
TAPT	triple antiplatelet therapy

Antithrombotic therapy is an important factor in improving the clinical outcomes of symptomatic PAD.⁴ The guidelines currently recommend that antiplatelet therapy including aspirin and clopidogrel be used for patients with symptomatic PAD; however, the evidence for antithrombotic therapy in the patients undergoing endovascular therapy (EVT) is less addressed.^{4,5} In brief, a patient who underwent EVT was recommended for at least 1 month of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel.⁵ However, there is a lack of evidence on optimal antithrombotic therapy after EVT in patients with diabetes who are expected to have worse outcomes.

Cilostazol, an antiplatelet agent with similar effects as those of ticlopidine and clopidogrel, is used to improve symptoms of the leg and walking impairment in

patients with PAD.^{6,7} However, a meta-analysis recently reported that cilostazol therapy benefits all limb-related and arterial patency-related outcomes and revealed the protective effect of cilostazol in the setting of DAPT in the subgroup analysis.⁸ In addition, although cilostazol is effective in improving platelet inhibition in patients irrespective of diabetes,⁹ various studies reported that the cilostazol had beneficial effects on stroke, coronary stent restenosis, and ischemic vascular events, especially in patients with diabetes.¹⁰⁻¹² In context, the use of cilostazol as a triple antiplatelet therapy (TAPT) combined with aspirin and clopidogrel is expected to be effective for patients with diabetes after EVT; however, the evidence regarding this is lacking.

Thus, the present study aimed to investigate the effect of TAPT on the clinical outcomes after EVT in patients with PAD accompanied by diabetes using a nationwide, multicenter, real-world registry.

METHODS

The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. The data are available upon reasonable request.

Study Population

The K-VIS ELLA (Korean Vascular Intervention Society Endovascular Therapy in the Lower Limb Artery Diseases) registry is a multicenter observational study with a retrospective and prospective cohort of patients with lower-extremity artery disease treated with endovascular therapy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02748226) NCT02748226). A detailed description of the K-VIS ELLA registry has been provided in a previous report.¹³ Briefly, a total of 3434 patients with 5097 affected limbs treated between January 2006 and July 2015 in 31 Korean hospitals were enrolled in the registry. The inclusion criteria were age ≥ 20 years and lower-extremity artery disease treated with EVT. Patients with acute limb ischemia, Buerger disease, and repeated revascularization after the first index procedure were excluded. From this registry population, 990 patients with diabetes (1286 limbs) who received DAPT (aspirin plus clopidogrel) after EVT were included in the current analysis (Figure 1). The 990 patients with diabetes were divided into 2 groups according to the use of cilostazol as an additional antiplatelet therapy (TAPT group, n=350 versus DAPT group, n=640). The data on patient demographics, baseline clinical and lesion characteristics, medication history, clinical presentation, laboratory test results, treatments, and follow-up outcomes were collected from electronic medical records. The study protocol was approved by the institutional review board of each hospital and was conducted according

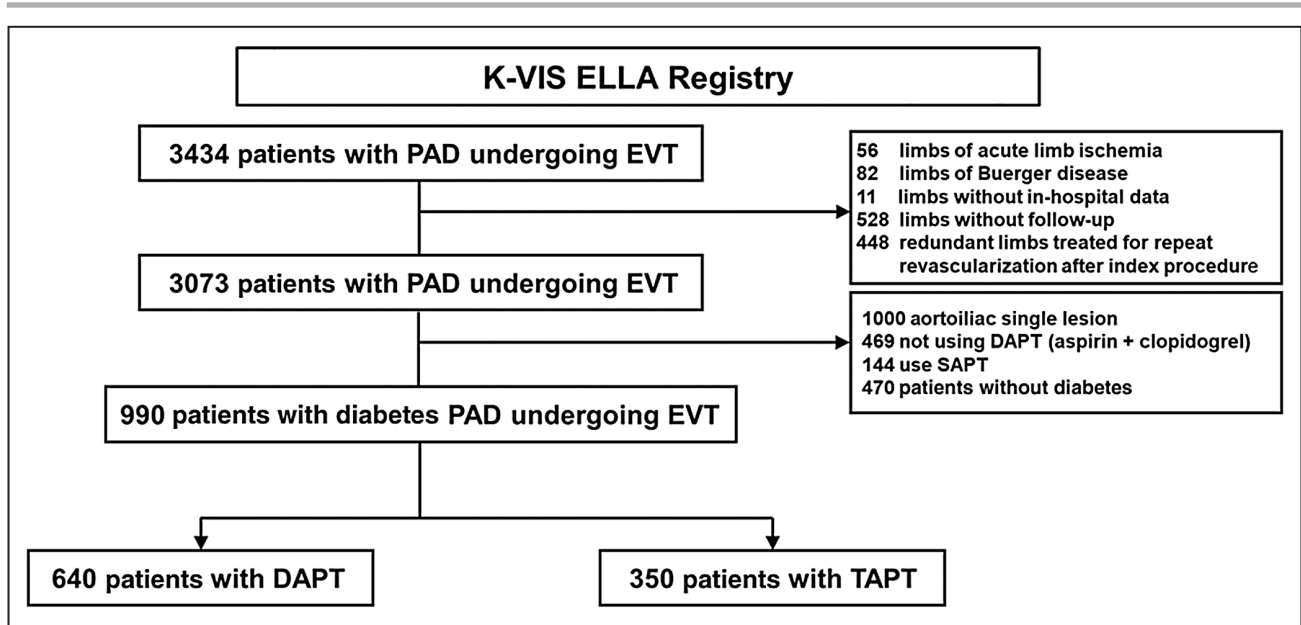


Figure 1. Flow chart.

DAPT indicates dual antiplatelet therapy; EVT, endovascular therapy; K-VIS ELLA, Korean Vascular Intervention Society Endovascular Therapy in the Lower Limb Artery Diseases; PAD, peripheral artery disease; SAPT, single antiplatelet therapy; and TAPT, triple antiplatelet therapy.

to the principles of the Declaration of Helsinki. The institutional review boards of the participating hospitals waived the requirement for informed consent because of the retrospective nature of the study.

Definitions and Study End Points

PAD was defined as the presence of $\geq 50\%$ narrowing of the lower-extremity artery. Claudication was defined as Rutherford category 1, 2, or 3 diseases, and critical limb ischemia (CLI) was defined as Rutherford category 4, 5, or 6 diseases.¹⁴ The presence of diabetes was identified by the patient’s history and medical records, including outpatient clinics and prescriptions of oral hypoglycemic agents or insulin. Technical success was defined as successful revascularization with residual stenosis $< 30\%$ and the absence of flow-limiting dissection or a hemodynamically significant translesion pressure gradient. Major amputations are those that occur proximal to the tarsometatarsal joint (Chopart, Boyd, Syme, below knee, and above knee), and a minor amputation was defined as occurring distal or through the tarsometatarsal joint (forefoot, transmetatarsal, and Lisfranc). The primary end points of this study were major adverse limb events (MALEs; a composite of major amputation, minor amputation, and reintervention). The secondary end points were all-cause mortality, major amputation, minor amputation, reintervention, and major bleeding. These outcomes were compared between the TAPT and DAPT groups.

Statistical Analysis

Continuous variables were expressed as mean \pm SD and were compared using Student’s *t* test for parametric data and the Mann–Whitney test for nonparametric data. Categorical variables were expressed as numbers (percentages) and were compared using the chi-square test or Fisher’s exact test. The data were analyzed on a per-patient basis for clinical characteristics and on a per-lesion basis for the limb, lesion, or procedural characteristics. Propensity score matching was performed to reduce the bias of baseline characteristics and potential confounding factors and to adjust for the significant differences in the patient characteristics. The propensity scores were estimated using a nonparsimonious multiple logistic regression model for TAPT. Age, sex, level of hemoglobin A_{1c}, hypertension, use of insulin, hypercholesterolemia, smoking status (current or former smoker), end-stage renal disease, history of coronary artery disease, history of congestive heart failure, history of stroke, history of EVT, history of bypass surgery, history of amputation, and each grade of Rutherford classification were selected to calculate the propensity score. A local optimal algorithm using the caliper method was used to develop propensity score–matched pairs without replacement (1:1 match). To ensure that poorly fitting matches were excluded, a matching caliper of 0.2 SDs from the estimated propensity score logit was enforced using MatchIt package from the R Core Team (R version 3.6.0; the R Foundation for Statistical Computing, Vienna, Austria;

<https://www.R-project.org/>). The cumulative incidences of clinical events were presented as Kaplan–Meier estimates and were compared using the log-rank test. Univariate Cox proportional hazards regression analyses using baseline clinical, lesion, and procedural variables were performed to identify the factors associated with clinical events. Variables with P values <0.20 in the univariate analysis were evaluated in the multivariate analysis model to determine the independent predictors of clinical events. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY). All the tests were 2-sided, and the statistical significance was set at $P<0.05$.

RESULTS

Baseline Characteristics

The baseline clinical characteristics of patients according to the antiplatelet regimen (DAPT versus TAPT) after discharge are summarized in Table 1. Of the 990 patients enrolled, 640 (64.6%) patients were categorized into the DAPT group (aspirin and clopidogrel), and 350

(35.4%) patients into the TAPT group (aspirin, clopidogrel, and cilostazol). The mean age of the entire cohort was 68.7 ± 8.7 years, and 762 (77.0%) patients were men. Compared with the patients in the DAPT group, those in the TAPT group were of lesser weight, had a higher prevalence of coronary artery disease, and had a lower prevalence of chronic kidney disease, end-stage renal disease, and previous amputation. Patients in the DAPT group were more likely to be diagnosed with critical limb ischemia on the basis of the Rutherford classification than those in the TAPT group. The use of insulin and hemoglobin A_{1c} levels did not differ between the 2 groups. To minimize the confounding factors, propensity score matching was performed, as described in Table S1.

Baseline Lesions and Procedural Characteristics and Complications

Table 2 demonstrates the baseline lesion and procedural characteristics according to the antiplatelet regimen after discharge. Compared with the DAPT group, the TAPT group had a lower ankle-brachial index and a higher prevalence of total occlusive lesions and

Table 1. Baseline Clinical Characteristics

	Total (N=990)	DAPT (N=640)	TAPT (N=350)	P value
Age, y	68.7±8.7	68.5±8.7	69.2±8.6	0.262
Sex, male	762 (77.0%)	490 (76.6%)	272 (77.7%)	0.739
Hemoglobin A_{1c} , %	7.7±1.6	7.7±1.7	7.6±1.6	0.289
Body mass index, kg/m ²	24.1±3.9	23.8±3.8	24.5±4.2	0.014*
Hypertension	785 (79.3)	501 (78.3)	284 (81.1)	0.327
Use of insulin	355 (35.9)	242 (37.8)	113 (32.3)	0.096
Hypercholesterolemia	357 (36.1)	242 (37.8)	115 (32.9)	0.138
Current or former smoker	491 (49.6)	315 (49.2)	176 (50.3)	0.790
Chronic kidney disease	305 (30.8)	220 (34.4)	85 (24.3)	0.001*
End-stage renal disease	201 (20.3)	152 (23.8)	49 (14.0)	<0.001*
Coronary artery disease	592 (59.8)	359 (56.1)	233 (66.6)	0.002*
Congestive heart failure	47 (4.7)	34 (5.3)	13 (3.7)	0.330
Previous history of stroke	155 (15.7)	103 (16.1)	52 (14.9)	0.674
Previous history of EVT	91 (9.2)	64 (10.0)	27 (7.7)	0.282
Previous history of bypass surgery	17 (1.7)	13 (2.0)	4 (1.1)	0.440
Previous history of amputation	99 (10.0)	78 (12.2)	21 (6.0)	0.003*
Rutherford classification				0.001*
1	83 (8.4)	49 (7.7)	34 (9.7)	
2	172 (17.4)	105 (16.4)	67 (19.1)	
3	199 (20.1)	116 (18.1)	83 (23.7)	
4	71 (7.2)	43 (6.7)	28 (8.0)	
5	264 (26.7)	201 (31.4)	63 (18.0)	
6	201 (20.3)	126 (19.7)	75 (21.4)	
Critical limb ischemia	536 (54.1)	370 (57.8)	166 (47.4)	0.002*

Values are presented as mean±standard deviation or number (%), unless otherwise stated. DAPT indicates dual antiplatelet therapy; EVT, endovascular therapy; and TAPT, triple antiplatelet therapy.

* $P<0.05$.

Table 2. Baseline Lesion and Procedural Characteristics

	Total	DAPT	TAPT	P value
	(N=1286)	(N=824)	(N=462)	
Ankle-brachial index	0.7±0.3	0.7±0.3	0.6±0.3	0.044*
TASC II classification				0.782
A	153 (11.9)	102 (12.4)	51 (11.0)	
B	272 (21.2)	177 (21.5)	95 (20.6)	
C	236 (18.4)	146 (17.7)	90 (19.5)	
D	625 (48.6)	399 (48.4)	226 (48.9)	
Number of target vessels	1.7±0.8	1.7±0.8	1.6±0.8	0.113
Target vessels				0.038*
Aortoiliac	130 (10.1)	81 (9.8)	49 (10.6)	
Femoropopliteal	789 (61.4)	488 (59.2)	301 (65.2)	
Infrapopliteal	367 (28.5)	255 (30.9)	112 (24.2)	
Total occlusion	565 (43.9)	342 (41.5)	223 (48.3)	0.022*
In-stent restenosis	38 (3.0)	19 (2.3)	19 (4.1)	0.096
Treatment modality				0.083
Balloon only	666 (51.8)	443 (53.8)	223 (48.3)	
Stent	577 (44.9)	351 (42.6)	226 (48.9)	
Others	43 (3.3)	30 (3.6)	13 (2.8)	
Lesion length, mm	138.2±107.1	143.5±110.5	128.2±99.9	0.020*
Diameter stenosis, %	89.4±13.3	88.9±13.8	90.3±12.5	0.063

Values are presented as mean±standard deviation or number (%), unless otherwise stated. DAPT indicates dual antiplatelet therapy; TAPT, triple antiplatelet therapy; and TASC II, Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II Classifications. *P<0.05.

femoropopliteal lesion. The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II classification and treatment modality did not differ between the 2 groups. The technical success rate, total in-hospital events, and immediate procedural complications did not differ between the 2 groups (Figure 2).

Follow-Up Clinical Outcomes and Independent Predictors

The mean follow-up duration was 499±253 days. The Kaplan–Meier curves illustrate MALEs and minor amputation stratified by each antiplatelet regimen. Albeit the TAPT group had a lower incidence of MALEs (16.6% versus 21.2%; log-rank P=0.045; Figure S1A) in the

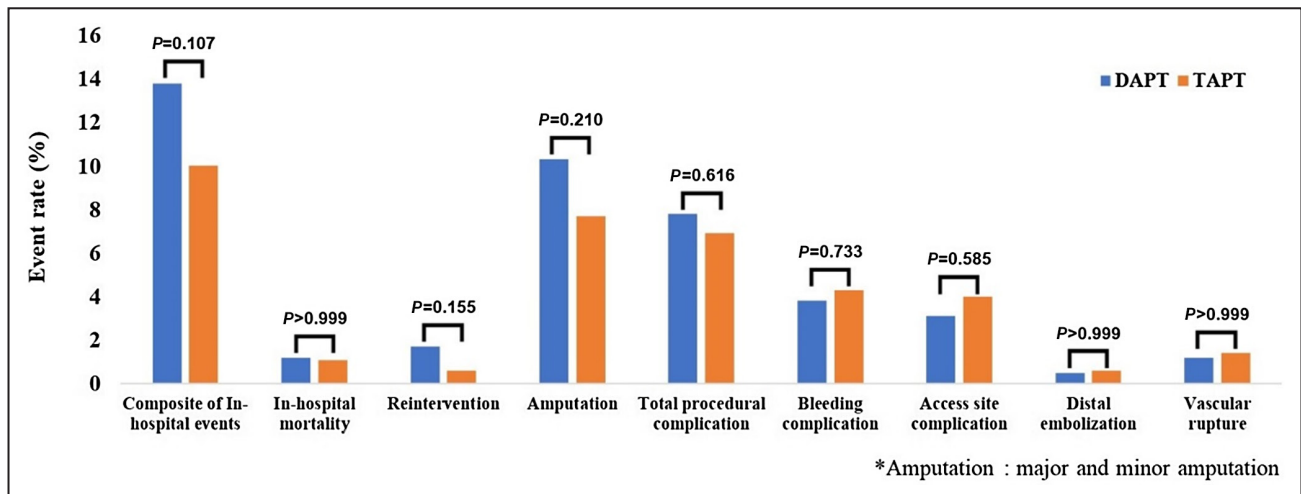


Figure 2. In-hospital outcomes and immediate procedural complications regarding antiplatelet regimen during index admission.

Crude incidence of death, reintervention, amputation, bleeding complication, access site complication, distal embolization, and vascular rupture for DAPT (blue) and TAPT (orange). DAPT indicates dual antiplatelet therapy; and TAPT, triple antiplatelet therapy.

unmatched study population, there was no difference in the MALEs between the 2 groups in the propensity score–matched study population (16.6% versus 19.4%; log-rank $P=0.260$; Figure 3A). However, regarding the minor amputation, the TAPT group had a lower incidence compared with the DAPT group in both the unmatched study population (2.0% versus 7.7%; log-rank $P<0.001$; Figure S1B) and the propensity score–matched study population (2.0% versus 6.3%; log-rank $P=0.004$; Figure 3B). No significant differences were observed between the 2 groups in terms of death (Figure S2A), major amputation (Figure S2B), reintervention (Figure S2C), or major bleeding (Figure S2D) during the follow-up period.

In the multivariate Cox regression model, end-stage renal disease (adjusted hazard ratio [HR], 2.011 [95% CI, 1.445–2.800]; $P<0.001$), coronary artery disease (adjusted HR, 0.717 [95% CI, 0.536–0.959]; $P=0.025$), and congestive heart failure (adjusted HR, 2.287 [95% CI, 1.387–3.772]; $P=0.001$) were independent predictors of MALEs (Table 3). The independent predictors for minor amputation during the follow-up were end-stage renal disease (adjusted HR, 2.348 [95% CI, 1.309–4.212]; $P=0.004$), history of amputation (adjusted HR, 1.872 [95% CI, 1.008–3.475]; $P=0.047$), CLI (adjusted HR, 4.769 [95% CI, 1.970–11.543]; $P=0.001$), and TAPT (adjusted HR, 0.354 [95% CI, 0.158–0.794]; $P=0.012$; Table 4). After

matching, TAPT remained as an independent predictor of minor amputation.

Influence of TAPT on the Clinical Outcomes According to the Initial Presentation

To assess the influence of additional cilostazol treatment as TAPT on the clinical outcomes according to the initial clinical presentation, we analyzed the data separately in patients with intermittent claudication or CLI (Figure 4). Among the patients with intermittent claudication, no difference was found in the incidence of MALEs between the DAPT and TAPT groups (Figure 4A). Meanwhile, among patients who presented with CLI, TAPT showed a tendency of lower incidence of MALEs than the DAPT group without statistical significance (17.5% versus 25.7%; log-rank P after Bonferroni correction=0.056; Figure 4B).

DISCUSSION

The present study reported the association between an additional treatment with cilostazol as one of the TAPT regimens and the clinical outcomes in patients with diabetes undergoing EVT for PAD. The TAPT group showed no significant difference in the incidence of MALEs compared with the DAPT group.

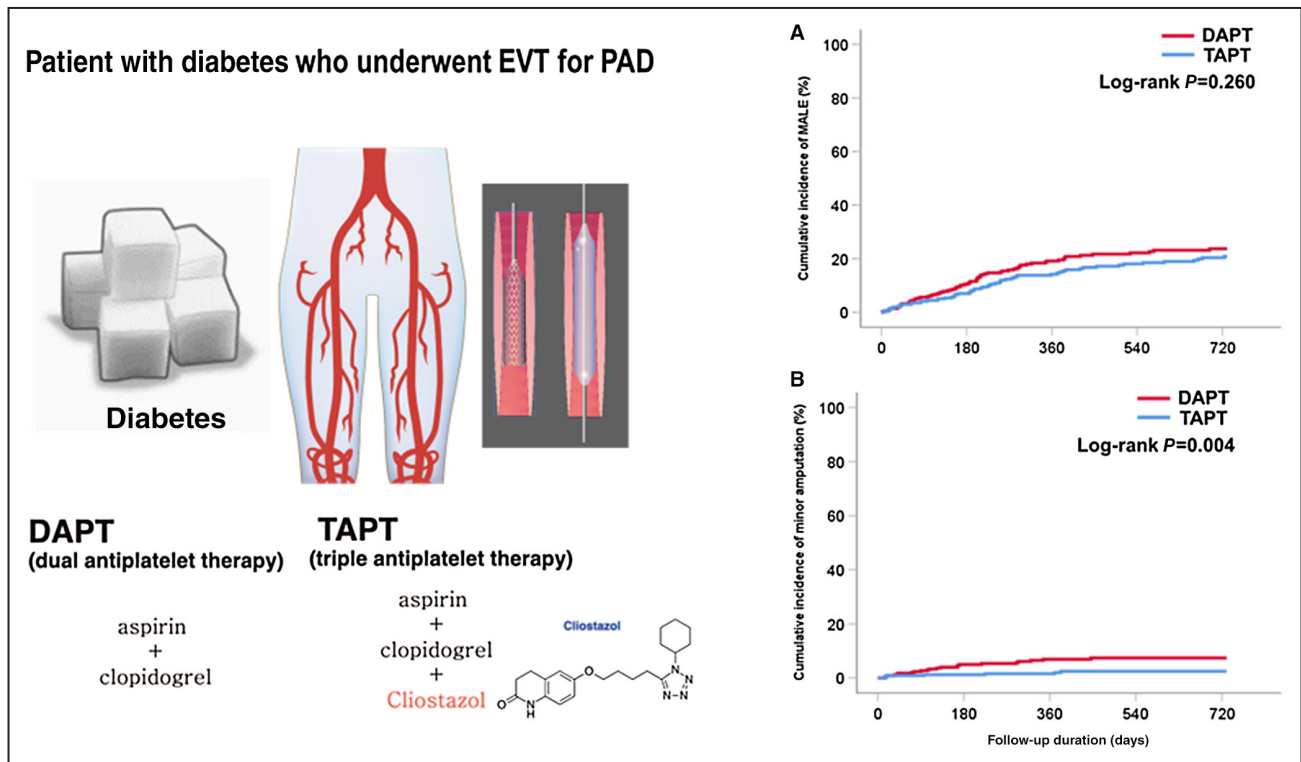


Figure 3. Comparison of the clinical outcomes between DAPT and TAPT in the propensity score–matched study population. A, Major adverse limb event; B, minor amputation. DAPT indicates dual antiplatelet therapy; EVT, endovascular therapy; MALE, major adverse limb event; PAD, peripheral artery disease; and TAPT, triple antiplatelet therapy.

Table 3. Independent Predictors of Major Adverse Limb Events

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age, per 10y	0.889	0.758–1.044	0.151	1.027	0.862–1.222	0.768
Sex, female	0.961	0.689–1.342	0.817			
Low body mass index, <18.5 kg/m ²	1.242	0.692–2.227	0.467			
Hypertension	1.002	0.712–1.410	0.991			
Use of insulin	1.521	1.147–2.018	0.004	1.243	0.924–1.672	0.150
Hypercholesterolemia	0.935	0.697–1.255	0.656			
End-stage renal disease	2.520	1.869–3.398	<0.001	2.011	1.445–2.800	<0.001*
Congestive heart failure	2.718	1.672–4.416	<0.001	2.287	1.387–3.772	0.001*
Current or former smoker	0.836	0.631–1.108	0.213			
Coronary artery disease	0.712	0.537–0.945	0.019	0.717	0.536–0.959	0.025*
Previous history of stroke	1.439	1.013–2.045	0.042	1.300	0.911–1.856	0.148
Previous history of bypass surgery	0.867	0.277–2.713	0.807			
Previous history of amputation	1.921	1.308–2.821	0.009	1.395	0.925–2.104	0.112
Previous history of EVT	1.466	0.956–2.248	0.079	1.372	0.883–2.132	0.160
Critical limb ischemia	1.694	1.263–2.271	0.004	1.354	0.989–1.855	0.059
Triple antiplatelet therapy	0.731	0.538–0.995	0.046	0.919	0.670–1.260	0.598

EVT indicates endovascular therapy; and HR, hazard ratio.

* $P < 0.05$.

However, the TAPT group showed a lower incidence of minor amputation with statistical significance than the DAPT group. In multivariable analysis, TAPT was an independent predictor of minor amputation during the follow-up period after EVT in patients with PAD.

Cilostazol selectively inhibits phosphodiesterase III and prevents stent thrombosis as an additional effect to DAPT after coronary interventions.^{15–17} In addition, cilostazol has antiproliferative effects on vascular smooth muscle cells and is known to prevent restenosis and angiogenesis after coronary stent insertion.^{11,18} However, for patients with PAD, the current guidelines addressed little evidence of better clinical outcomes regarding cilostazol, with only some favorable effects on the walking distance and improvement of claudication.^{4,5}

Several reports have addressed the clinical impact of cilostazol on adverse limb events. Nanto et al¹⁹ reported that patients with cilostazol as an additional treatment had improved primary patency compared with those without cilostazol in 2737 patients who underwent EVT for PAD. A meta-analysis of patients who underwent EVT also reported an improvement in the primary patency and risk reduction of amputation or reintervention in patients with cilostazol.²⁰ Another report, which included elderly patients and investigated the association between cilostazol and limb salvage after endovascular or open surgery for PAD, showed a decrease in the amputation rate in patients using

cilostazol.²¹ In our results, the TAPT group exhibited lower rates of MALEs and minor amputation compared with the DAPT group; however, there was no difference in the reintervention. A plausible explanation is that the aforementioned studies included patients without diabetes. In addition, in our study, since all enrolled patients used DAPT after EVT, cilostazol may not have an additional effect on the reduction of intervention rate.

Although various studies have reported the impact of cilostazol in terms of restenosis in coronary artery interventions in patients with diabetes,^{16,18,22} studies on the effect of cilostazol on PAD in patients with diabetes are lacking. Recently, Kalantzi et al¹² reported a randomized study that investigated the efficacy and safety of adjunctive cilostazol to clopidogrel-treated patients with type 2 diabetes exhibiting lower-extremity arterial disease. In that report, the patient who was treated with adjunctive cilostazol to clopidogrel benefited from ischemic events and showed an improvement in the claudication symptoms, without an increase in the bleeding risk.¹² In addition, elderly patients undergoing lower extremity revascularization had a significant benefit from taking cilostazol, especially in patients with diabetes.²¹ Cilostazol had an enhanced effect in patients with diabetes in terms of the reduction of platelet reactivity and vasodilatory effect on peripheral circulation compared with that in individuals without diabetes.^{9,23} Similar to these studies, our results showed the

Table 4. Independent Predictors of Minor Amputation

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age, per 10y	0.797	0.595–1.068	0.129	1.004	0.717–1.406	0.982
Sex, female	0.982	0.528–1.827	0.955			
Low body mass index, <18.5 kg/m ²	1.727	0.689–4.329	0.243			
Hypertension	1.939	0.878–4.282	0.101	2.105	0.934–4.742	0.072
Use of insulin	2.075	1.227–3.509	0.006	1.434	0.827–2.485	0.199
Hypercholesterolemia	0.525	0.283–0.977	0.042	0.842	0.442–1.604	0.602
End-stage renal disease	4.472	2.646–7.558	<0.001	2.348	1.309–4.212	0.004*
Congestive heart failure	2.917	1.250–6.808	0.013	2.245	0.932–5.410	0.071
Current or former smoker	0.772	0.456–1.307	0.335			
Coronary artery disease	0.522	0.308–0.885	0.016	0.616	0.359–1.057	0.078
Previous history of stroke	1.064	0.522–2.171	0.864			
Previous history of bypass surgery	0.951	0.132–6.871	0.960			
Previous history of amputation	3.445	1.907–6.223	<0.001	1.872	1.008–3.475	0.047*
Previous history of EVT	1.482	0.671–3.272	0.330			
Critical limb ischemia	7.475	3.21–17.434	<0.001	4.769	1.97–11.543	0.001*

EVT indicates endovascular therapy; and HR, hazard ratio.
*P<0.05.

clinical benefit of adjuvant cilostazol in terms of minor amputations.

An optimal strategy for antiplatelet therapy in patients undergoing EVT for PAD has not yet been established. The current guidelines recommend single antiplatelet therapy to prevent adverse clinical outcomes in patients undergoing EVT for PAD. DAPT is generally recommended for at least 1 month.^{4,5} Recently, Cho et al²⁴ reported that the long-term use

of DAPT might benefit the clinical outcomes regarding cardiac or vascular events without increasing the bleeding risk in patients with PAD who underwent EVT. In context, TAPT can be expected to be more effective in reducing ischemic events compared with DAPT in cases with a similar rate of bleeding events. As expected to the safety concern, the rate of major bleeding and in-hospital complication of the present study did not differ between the TAPT and DAPT groups.

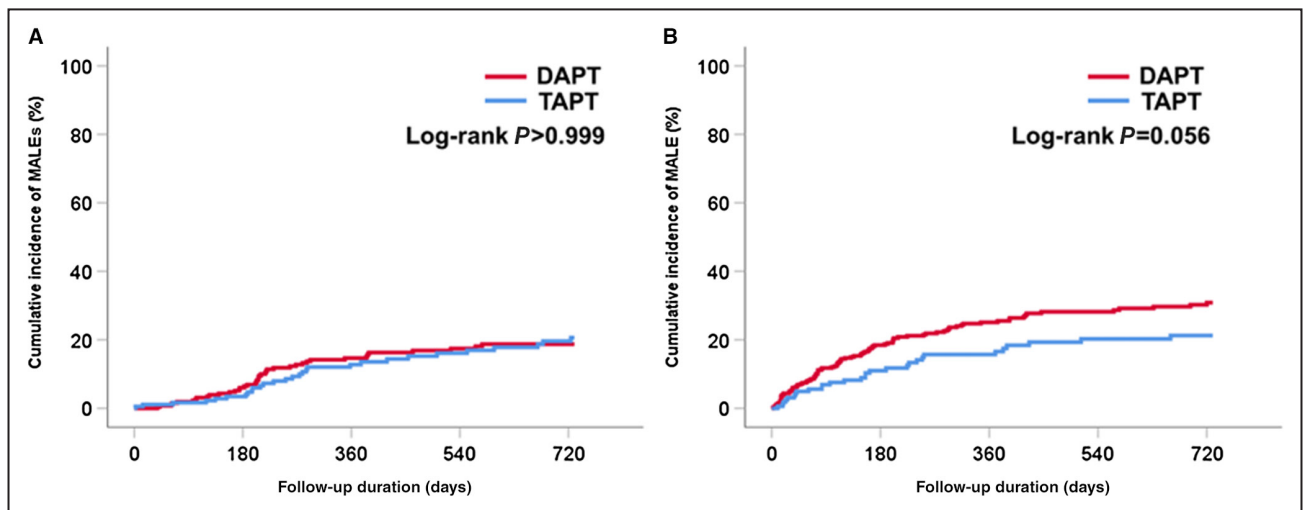


Figure 4. Comparison of the clinical outcomes of TAPT according to initial clinical presentation in the unmatched study population.

A, Intermittent claudication; **(B)** critical limb ischemia. DAPT indicates dual antiplatelet therapy; MALEs, major adverse limb events; and TAPT, triple antiplatelet therapy.

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Meanwhile, the TAPT group showed a lower rate of adverse limb events than the DAPT group, and this difference mostly occurred within 6 months after EVT. In the present analysis, however, a relationship between TAPT and MALEs was not significant after multivariable adjustment for differences in baseline and lesion characteristics. It can be explained by a lack of power to achieve significant correlation between TAPT and MALEs. Also, the differences in MALE regarding TAPT were primarily attributable to a lower risk of minor amputations. However, our finding may support a useful option of TAPT including cilostazol as the initial treatment in patients with diabetes undergoing EVT.

When our data were analyzed separately in the 2 groups according to the initial presentation, TAPT did not significantly reduce the incidence of MALEs or minor amputation in patients with diabetes with intermittent claudication. However, a probability of benefits attributable to TAPT in reducing the risk of MALEs and minor amputation was observed only in patients with diabetes presenting with CLI. A recent study evaluated the association between cilostazol treatment and the clinical outcomes and predictive factors in patients with diabetes and CLI after endovascular revascularization of the affected angiosome.²⁵ Similar to our findings, the decreased risk of adverse limb events in patients with TAPT was observed only in patients with CLI.²⁵ However, the present study showed that there was no statistically significant difference in both claudication and CLI as well as no significant *P*-interaction. Thus, these results should be interpreted with caution.

This study has several limitations. First, given the retrospective nature of the study, causal relationships could not be determined. Therefore, prospective randomized trials will be required to validate the role of TAPT in the reduction of adverse limb events in patients with diabetes and PAD undergoing EVT. Second, although the enrolled patients were classified according to the Rutherford classification and we tried to minimize the confounding factors using propensity score matching, the association between the effect of EVT and unmeasured variables in terms of angiosomes or wound characteristics was not investigated. Thus, these results should be interpreted with caution. Finally, the optimal duration of TAPT was beyond the scope of this study. However, the individual antiplatelet regimen at discharge was observed to be generally maintained for at least 3 months. Finally, despite the limitation of the registry study, the present study was the first large-scale observation to use a nationwide, multicenter, real-world registry, which investigated the clinical impact of TAPT compared with that of DAPT in patients with diabetes undergoing EVT for PAD. Based on our findings, TAPT is an important topic to be addressed in future studies to establish an optimal antiplatelet therapy strategy.

CONCLUSIONS

In patients with diabetes undergoing EVT for PAD, compared with DAPT, TAPT showed no significant differences in the incidence of MALEs but would provide the benefit of reduced risk of minor amputation. Future research will be required to determine whether TAPT can improve the clinical outcomes after EVT in patients with diabetes and PAD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline clinical characteristics after PSM

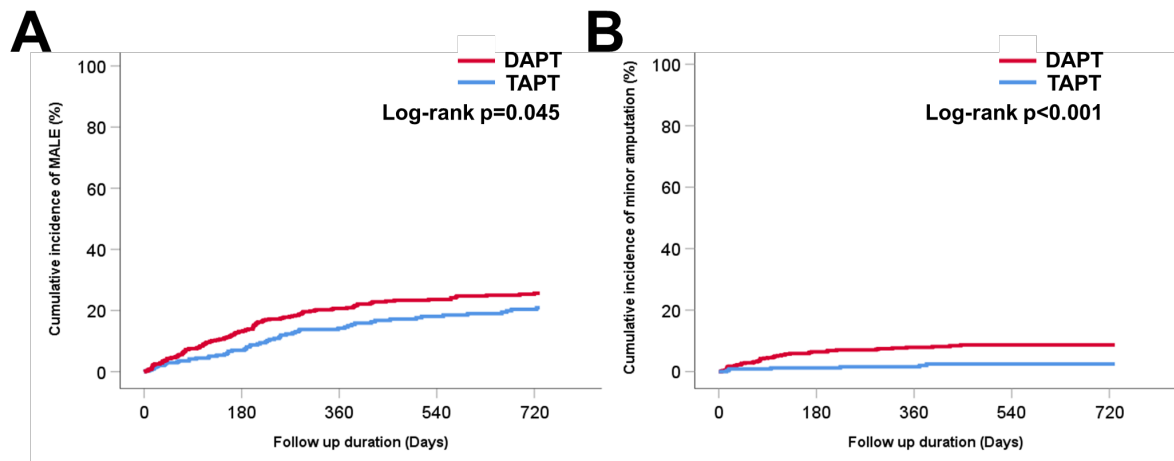
	Total (N=700)	DAPT (N=350)	TAPT (N=350)	p
Age (years)	69.2 ± 8.7	69.3 ± 8.8	69.2 ± 8.6	0.855
Male	546 (78.0%)	274 (78.3%)	272 (77.7%)	0.927
Hemoglobin A1c (%)	7.6 ± 1.6	7.7 ± 1.7	7.6 ± 1.6	0.443
BMI (kg/m²)	24.2 ± 4.0	24.0 ± 3.8	24.5 ± 4.2	0.116
Hypertension	569 (81.3%)	285 (81.4%)	284 (81.1%)	1.000
Use of Insulin	224 (32.0%)	111 (31.7%)	113 (32.3%)	0.935
Hypercholesterolemia	241 (34.4%)	126 (36.0%)	115 (32.9%)	0.426
Current or Ex-smoker	361 (51.6%)	185 (52.9%)	176 (50.3%)	0.545
Chronic kidney disease	169 (24.1%)	84 (24.0%)	85 (24.3%)	1.000
End-stage renal disease	90 (12.9%)	41 (11.7%)	49 (14.0%)	0.429
Coronary artery disease	455 (65.0%)	222 (63.4%)	233 (66.6%)	0.428
Congestive heart failure	28 (4.0%)	15 (4.3%)	13 (3.7%)	0.847
Previous history of stroke	106 (15.1%)	54 (15.4%)	52 (14.9%)	0.916
Previous history of EVT	55 (7.9%)	28 (8.0%)	27 (7.7%)	1.000
Previous history of bypass surgery	8 (1.1%)	4 (1.1%)	4 (1.1%)	1.000
Previous history of amputation	43 (6.1%)	22 (6.3%)	21 (6.0%)	1.000

	Total (N=700)	DAPT (N=350)	TAPT (N=350)	p
Rutherford classification				0.901
1	74 (10.6%)	40 (11.4%)	34 (9.7%)	
2	139 (19.9%)	72 (20.6%)	67 (19.1%)	
3	169 (24.1%)	86 (24.6%)	83 (23.7%)	
4	57 (8.1%)	29 (8.3%)	28 (8.0%)	
5	119 (17.0%)	56 (16.0%)	63 (18.0%)	
6	142 (20.3%)	67 (19.1%)	75 (21.4%)	
Critical limb ischemia	318 (45.4%)	152 (43.4%)	166 (47.4%)	0.324

Values are presented as mean \pm standard deviation or number (%), unless otherwise stated.

BMI, body mass index; *DAPT*, dual antiplatelet therapy; *EVT* endovascular therapy; *MALE*, major adverse limb events; *PSM*, propensity score matching; *TAPT*, triple antiplatelet therapy

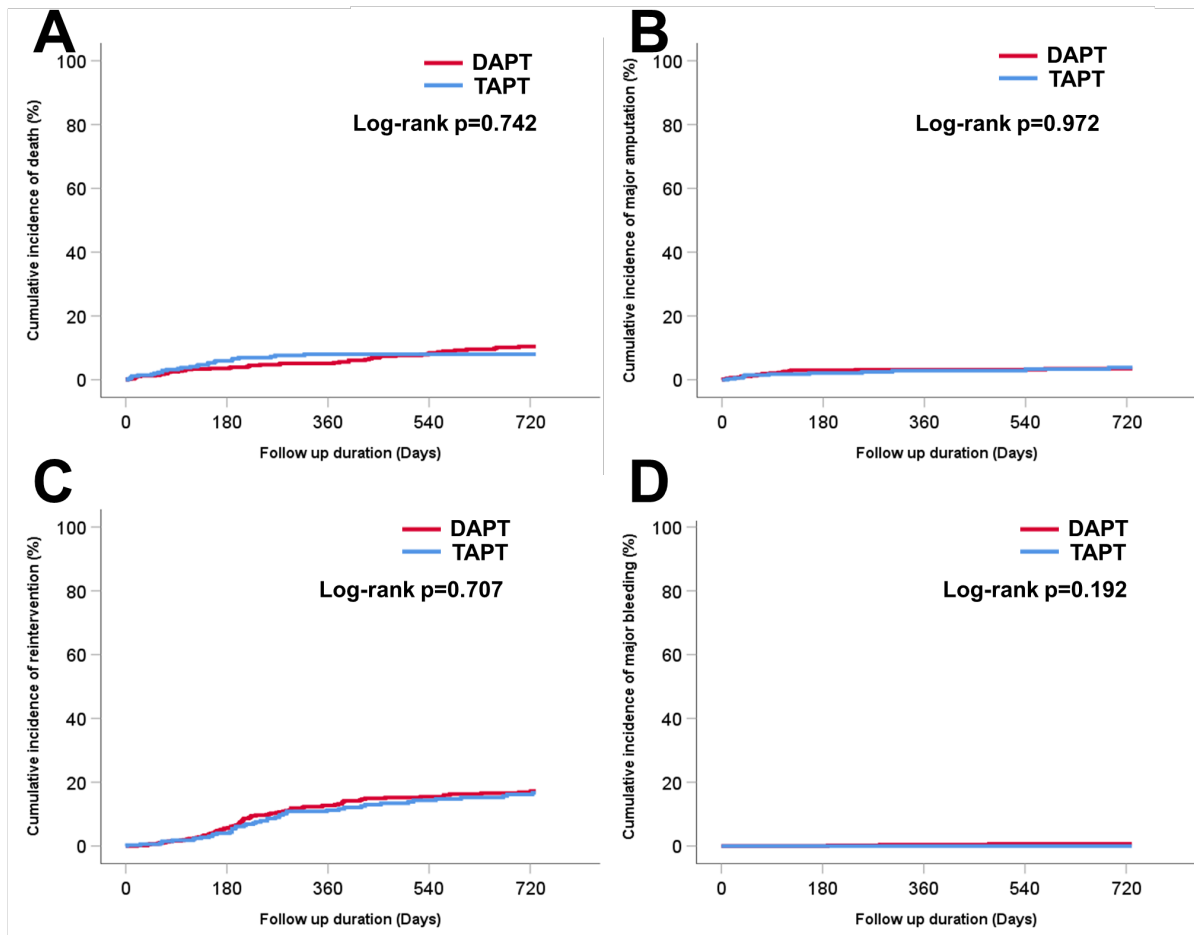
Figure S1. Comparison of the clinical outcomes between DAPT and TAPT in the unmatched study population



a. MALE, b. minor amputation.

DAPT, dual antiplatelet therapy; *MALE*, major adverse limb events; *TAPT*, triple antiplatelet therapy

Figure S2. Comparison of the clinical outcomes between DAPT and TAPT in the unmatched study population



a. all-cause death, b. major amputation, c. reintervention, d. major bleeding.

DAPT, dual antiplatelet therapy; *TAPT*, triple antiplatelet therapy