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Original Article

Comparison of Single Antiplatelet Therapy and Dual Antiplatelet Therapy after Endovascular Therapy in Patients with Lower Extremity Artery Disease

Takehiro Yamada, MD,[1] Takahiro Tokuda, MD,[2] Naoki Yoshioka, MD, PhD,[3] Akio Koyama, MD,[4] Ryusuke Nishikawa, MD,[5] Kiyotaka Shimamura, MD,[6] and Takuma Aoyama, MD, PhD[1,7]

Objectives: Evidence for antithrombotic therapy after endovascular therapy (EVT) is limited.
Methods: This retrospective, multicenter, observational study enrolled 732 consecutive patients with lower extremity artery disease who underwent EVT between January 2018 and December 2019. Overall, 570 patients who received single antiplatelet therapy (SAPT) and dual antiplatelet therapy (DAPT) were selected and divided into the SAPT (n = 189) and DAPT (n = 381) groups. The primary outcome was bleeding events at 24 months. The secondary outcomes were bleeding events at 30 days and 24 months after 30 days, ischemic events, and all-cause death at 24 months. Bleeding and ischemic events at 24 months were investigated in subgroups.
Results: A propensity score matching yielded 164 patients in both groups. There were no significant differences in bleeding events between the SAPT and DAPT groups (14.2% and 11.3% at 24 months, p = 0.775; 2.5% and 6.1% at 30 days, p = 0.106; 11.7% and 6.7% at 24 months after 30 days, p = 0.162). Additionally, there was no significant difference in ischemic events at 24 months between the two groups (32.7% and 30.6%, p = 0.625). Bleeding and ischemic events at 24 months were similar between subgroups.
Conclusions: No significant differences in bleeding or ischemic events between SAPT and DAPT were observed.

Keywords: lower extremity artery disease, endovascular therapy, antithrombotic therapy, single antiplatelet therapy, dual antiplatelet therapy

Introduction

Antithrombotic therapy (AT) is administered to patients with lower extremity artery disease (LEAD) to prevent limb-related and general cardiovascular events in the future. Two previous randomized controlled trials (RCTs) did not show the cardiovascular clinical benefit of aspirin monotherapy for asymptomatic LEAD,[1,2] whereas, for symptomatic LEAD, AT contributed to the reduction of cardiovascular events.[3–5] Although dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is not related to the prevention of adverse limb events after bypass surgery,[6] several studies have reported a significant reduction in target lesion revascularization (TLR), major adverse cardiovascular events (MACE), or major adverse limb events of DAPT after endovascular therapy (EVT).[7–9]

However, antithrombotic agents carry an increased risk of bleeding, and risk reduction of bleeding is an important issue in AT. A recent report indicated the efficacy and safety of dual pathway inhibition (DPI) of aspirin and low-dose rivaroxaban.[10] Additionally, the efficacy and safety of DPI have been consistent in the post-revascularization phase, and the VOYAGER PAD trial showed that DPI significantly reduced adverse cardiovascular and limb

[1]*Division of Cardiology, Central Japan International Medical Center, Minokamo, Gifu, Japan*
[2]*Division of Cardiology, Nagoya Heart Center, Nagoya, Aichi, Japan*
[3]*Division of Cardiology, Ogaki Municipal Hospital, Ogaki, Gifu, Japan*
[4]*Division of Vascular Surgery, Toyota Memorial Hospital, Toyota, Aichi, Japan*
[5]*Division of Cardiology, Kyoto University Hospital, Kyoto, Kyoto, Japan*
[6]*Division of Cardiology, Osaka Red Cross Hospital, Osaka, Osaka, Japan*
[7]*Division of Molecular Pathology, Shinshu University of Medicine, Matsumoto, Nagano, Japan*

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Corresponding author: Takehiro Yamada, MD. Division of Cardiology, Central Japan International Medical Center, 1-1, Kenko-no-machi, Minokamo, Gifu 505-8510, Japan
Tel: +81-574-66-1100
E-mail: t.yamada1104@gmail.com

events without increasing the risk of major bleeding compared to aspirin monotherapy.[11] However, the VOYAGER PAD trial included both post-bypass surgery and post-endovascular revascularization populations. Therefore, the results of the VOYAGER PAD trial did not clearly demonstrate the efficacy and safety of DPI in patients with post-endovascular revascularization only.

The current guidelines recommend DAPT for at least 1 month after endovascular revascularization, especially after post-stenting.[12–15] Although DAPT has been reported to reduce TLR 6 months after EVT compared to single antiplatelet therapy (SAPT),[7] the evidence of AT after EVT has been limited. Moreover, no reports have directly compared bleeding and ischemic events between SAPT and DAPT after EVT.

Materials and Methods

Participants

We analyzed the ASIGARU PAD registry database, which is an ongoing multi-center observational registry. This registry includes consecutive patients with LEAD who underwent EVT between January 2018 and December 2019 at 6 institutions in Japan. The inclusion criteria were as follows: aged ≥20 years, patients with symptomatic LEAD of Rutherford category 2–6, and de novo or recurrent stenotic or occlusive lesions. Patients who underwent EVT for acute limb ischemia (ALI), traumatic complications, or aortic dissection were excluded. Hybrid therapy with EVT and open surgical procedures was also excluded. Patients who underwent multiple EVTs during the study period were enrolled only for the first procedure. Consequently, 732 consecutive patients were enrolled in this registry. From the registry population, 570 patients who received SAPT and DAPT were extracted and divided into 2 groups: 189 patients in the SAPT group and 381 patients in the DAPT group.

Medication and procedure protocol

Based on the current guidelines,[12–15] at least one antithrombotic agent was administered before EVT as the initial AT. The type, number, and duration of antithrombotic agents were adjusted according to the physician's discretion, considering the patient's comorbidities, and bleeding risk. Notably, aspirin, clopidogrel, and prasugrel were selected as the antiplatelet agents. The common femoral, brachial, and radial arteries were used as the primary access sites for EVT. If necessary, retrograde approaches, such as distal superficial femoral artery puncture, popliteal artery puncture, or below-knee (BK) artery puncture, were added. After sheath insertion, an intra-arterial or intravenous heparin bolus was administered as an anticoagulant during the procedure in all cases. The heparin dose was left to the investigators' discretion, and the activated clotting time was controlled between 250 and 300 s. The selection of the finalizing devices was decided according to the physician's discretion. Hemostasis was achieved at the puncture site using manual compression and/or a closure device.

Follow-up protocol

Clinical follow-up was conducted at baseline, 1, 3, 6, 12, 18, and 24 months, respectively. At each visit, patients were asked about the presence of bleeding and ischemic events.

Study outcome

The primary outcome measure was a bleeding event at 24 months. The secondary outcome measures were bleeding events at 30 days and 24 months after 30 days, ischemic events at 24 months, and all-cause death at 24 months. Bleeding and ischemic events at 24 months in each subgroup by diabetes mellitus (DM), hemodialysis, chronic limb-threatening ischemia (CLTI), and treatment segments were also investigated in this study.

Definition

LEAD was defined as an atherosclerotic occlusive disease of the lower extremity artery.[12] CLTI was defined according to the following criteria: (1) ischemic rest pain with confirmatory hemodynamic studies, (2) diabetic foot ulcer or any lower limb ulceration present for at least two weeks, and (3) gangrene involving any portion of the lower limb or foot.[14] The severity of frailty was categorized into three groups based on the Clinical Frailty Scale (CFS): 1–3 (well activities), 4–5 (mild frailty), and 6–8 (moderate or severe frailty).[16] SAPT was defined as any one of aspirin 100 mg daily, clopidogrel 75 mg daily, or prasugrel 3.75 mg daily. DAPT was defined as aspirin 100 mg plus clopidogrel 75 mg daily or aspirin 100 mg plus prasugrel 3.75 mg daily. AT was identified at discharge after EVT. Bleeding events were defined as bleeding academic research consortium (BARC) type-3 or type-5 bleeding.[17] BARC type-3 was defined as clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses as follows: any transfusion with overt bleeding, overt bleeding plus a hemoglobin drop ≥3 g/dL, cardiac tamponade, bleeding requiring surgical intervention or intravenous vasoactive drugs, or intracranial hemorrhage.[17] BARC type-5 was defined as fatal bleeding that directly causes death, with no other explainable cause.[17] Ischemic events were defined as the occurrence of ALI, myocardial infarction, stroke, or acute ischemic injury to any other organ.

Statistical analysis

Continuous data are presented as the mean ± standard deviation. Categorical data are presented as counts

(percentages). An unpaired t-test was used to compare the continuous variables, and the chi-square test was used for categorical data. The patients in the SAPT group were matched to those in the DAPT group in a 1:1 ratio. The covariates entered into the propensity score were age, sex, body mass index, DM, hypertension, dyslipidemia, hemodialysis, current smoking, CFS, history of heart failure, atrial fibrillation, history of myocardial infarction, prior percutaneous coronary intervention (PCI), prior coronary artery bypass graft (CABG), history of LEAD, history of cerebral infarction, history of intracranial hemorrhage, CLTI, and aortoiliac (AI), femoropopliteal (FP), and BK lesions. The nearest-neighbor method with a caliper width of 0.2 on the logit of the propensity score was used for matching. Prognostic outcomes were assessed using the Kaplan–Meier method, and differences between the groups were assessed using the log-rank test. Bleeding events at 30 days (perioperative period) and 24 months after 30 days (after the perioperative period) were studied using a landmark analysis. All p-values were two-tailed, with a p-value <0.05 considered statistically significant for all analyses. We used R (version 4.1.1) (the R-project for Statistical Computing [http://www.R-project.org/]) for all statistical analyses.

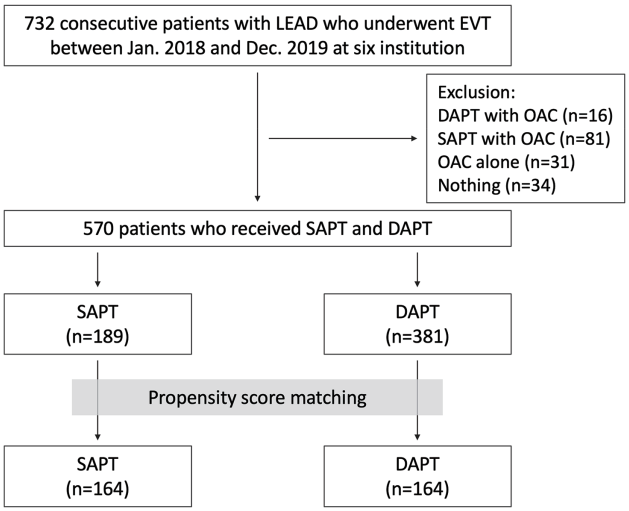


Fig. 1 Study flow diagram. DAPT: dual antiplatelet therapy; EVT: endovascular therapy; LEAD: lower extremity artery disease; OAC: oral anticoagulant; SAPT: single antiplatelet therapy

Results

Matching

The flow diagram of the study is shown in **Fig. 1**. Propensity score matching successfully identified 164 patients in both the SAPT and DAPT groups. The baseline patient and lesion characteristics before and after matching are shown in **Table 1**. In the pre-matched population, the mean age of the patients in the SAPT and DAPT groups was 75.6 and 73.8 years, respectively. Notably, 65.6% and 70.9% were male, 57.7% and 55.6% had DM, 33.9% and 28.1% were dialysis dependent, 19.6% and 13.9% had a history of heart failure, and 37.0% and 28.6% had CLTI, respectively. The median duration term of DAPT was 8.7 months (interquartile range: 2.9–24.9). The percentages of target lesions in the SAPT and DAPT groups were 35.4% and 41.5% for aortoiliac lesions, 63.5% and 65.4% for femoropopliteal lesions, and 28.0% and 10.2% for BK lesions, respectively. Before matching, there were significant differences in age, dyslipidemia, CFS, prior PCI, prior CABG, prior LEAD, CLTI, and BK lesions. However, after matching, all factors were well-balanced between the two groups.

Bleeding events at 30 days and 24 months

The Kaplan–Meier estimate showed a cumulative bleeding event rate of 14.2% in the SAPT group and 11.3% in the DAPT group at 24 months (p = 0.775; **Fig. 2**). A landmark analysis showed that the rates of cumulative bleeding events in the SAPT and DAPT groups were 2.5% and 6.1% at 30 days (p = 0.106), and 11.7% and 6.7% at 24 months after 30 days, respectively (p = 0.162; **Fig. 2**). Details of bleeding events are shown in **Table 2**.

Ischemic events at 24 months

The rates of cumulative ischemic events estimated using the Kaplan–Meier method were 32.7% in the SAPT group and 30.6% in the DAPT group at 24 months (p = 0.625; **Fig. 3**). Details of ischemic events are shown in **Table 2**.

Bleeding and ischemic events in each subgroup at 24 months

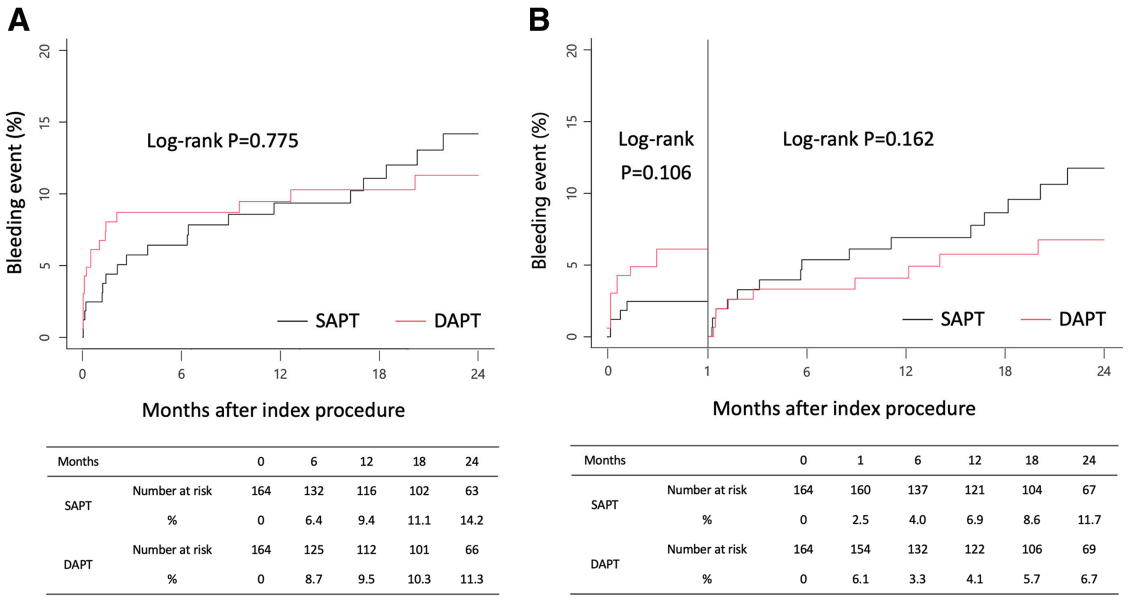
Bleeding and ischemic events in each subgroup according to DM, hemodialysis, CLTI, and treatment segments at 24 months are shown in **Figs. 4** and **5**. Bleeding events at 24 months between the SAPT and DAPT groups occurred at 10.6% and 11.4% and 17.1% and 11.2% in the non-DM and DM groups, respectively (p = 0.685 and p = 0.472); 11.2% and 7.2% and 22.0% and 27.0% in the non-hemodialysis and hemodialysis groups (p = 0.442 and p = 0.57); 8.9% and 9.2% and 25.7% and 15.2% in the non-CLTI and CLTI groups, respectively (p = 0.735 and p = 0.453); and 11.9% and 11.7%, 14.6% and 9.8%, and 24.9% and 17.9% in the AI, FP, and BK segments, respectively (p = 0.969, p = 0.698, and p = 0.721; **Fig. 4**). Ischemic events at 24 months between the SAPT and DAPT groups occurred at 26.7% and 24.7% and 37.2% and 34.8% in the non-DM and DM groups, respectively (p = 0.941 and p = 0.535); 29.4% and 25.3% and 40.7% and 49.1% in the non-hemodialysis and hemodialysis

Table 1 Baseline characteristics

	Before propensity matched				Propensity matched			
	Overall (n = 570)	SAPT (n = 189)	DAPT (n = 381)	p-Value	Overall (n = 328)	SAPT (n = 164)	DAPT (n = 164)	p-Value
Patient characteristics								
Age, years	74.4 ± 9.4	75.6 ± 9.8	73.8 ± 9.1	0.032	75.3 ± 9.5	74.9 ± 9.6	75.8 ± 9.3	0.385
Male gender, n (%)	394 (69.1)	124 (65.6)	270 (70.9)	0.211	222 (67.7)	110 (67.1)	112 (68.3)	0.906
BMI, kg/m^2	22.1 ± 3.6	21.9 ± 3.5	22.3 ± 3.7	0.214	22.0 ± 3.6	22.0 ± 3.4	22.0 ± 3.7	0.808
Diabetes mellitus, n (%)	321 (56.3)	109 (57.7)	212 (55.6)	0.655	186 (56.7)	90 (54.9)	96 (58.5)	0.577
Hypertension, n (%)	446 (78.2)	146 (77.2)	300 (78.7)	0.746	263 (80.2)	127 (77.4)	136 (82.9)	0.268
Dyslipidemia, n (%)	349 (61.2)	100 (52.9)	249 (65.4)	0.005	197 (60.1)	93 (56.7)	104 (63.4)	0.26
Hemodialysis, n (%)	171 (30.0)	64 (33.9)	107 (28.1)	0.174	95 (29.0)	51 (31.1)	44 (26.8)	0.465
Current smoker, n (%)	141 (24.7)	41 (21.7)	100 (26.2)	0.258	68 (20.7)	38 (23.2)	30 (18.3)	0.34
CFS, n (%)				0.001				0.416
1–3	289 (50.7)	77 (40.7)	212 (55.6)		138 (42.1)	75 (45.7)	63 (38.4)	
4–5	182 (31.9)	66 (34.9)	116 (30.4)		121 (36.9)	57 (34.8)	64 (39.0)	
6–8	99 (17.4)	46 (24.3)	53 (13.9)		69 (21.0)	32 (19.5)	37 (22.6)	
History of heart failure, n (%)	90 (15.8)	37 (19.6)	53 (13.9)	0.088	56 (17.1)	31 (18.9)	25 (15.2)	0.463
Atrial fibrillation, n (%)	38 (6.7)	15 (7.9)	23 (6.0)	0.38	24 (7.3)	12 (7.3)	12 (7.3)	1
History of myocardial infarction, n (%)	65 (11.4)	21 (11.1)	44 (11.5)	1	33 (10.1)	20 (12.2)	13 (7.9)	0.271
Prior PCI, n (%)	205 (36.0)	52 (27.5)	153 (40.2)	0.003	85 (25.9)	46 (28.0)	39 (23.8)	0.45
Prior CABG, n (%)	57 (10.0)	26 (13.8)	31 (8.1)	0.039	42 (12.8)	21 (12.8)	21 (12.8)	1
History of LEAD, n (%)	163 (28.6)	65 (34.4)	98 (25.7)	0.038	103 (31.4)	54 (32.9)	49 (29.9)	0.634
History of cerebral infarction, n (%)	113 (19.8)	44 (23.3)	69 (18.1)	0.148	66 (20.1)	35 (21.3)	31 (18.9)	0.68
History of intracranial hemorrhage, n (%)	18 (3.2)	4 (2.1)	14 (3.7)	0.447	7 (2.1)	4 (2.4)	3 (1.8)	1
CLTI, n (%)	179 (31.4)	70 (37.0)	109 (28.6)	0.044	112 (34.1)	54 (32.9)	58 (35.4)	0.727
Aspirin use, n (%)	496 (87.0)	115 (60.8)	381 (100.0)	<0.001	261 (79.6)	97 (59.1)	164 (100.0)	<0.001
P2Y12 inhibitor use, n (%)	455 (79.8)	74 (39.2)	381 (100.0)	<0.001	231 (70.4)	67 (40.9)	164 (100.0)	<0.001
Cilostazol use, n (%)	125 (21.9)	87 (46.0)	38 (10.0)	<0.001	90 (27.4)	78 (47.6)	12 (7.3)	<0.001
Lesion characteristics								
AI lesion, n (%)	225 (39.5)	67 (35.4)	158 (41.5)	0.173	133 (40.5)	66 (40.2)	67 (40.9)	1
FP lesion, n (%)	369 (64.7)	120 (63.5)	249 (65.4)	0.71	212 (64.6)	105 (64.0)	107 (65.2)	0.908
BK lesion, n (%)	92 (16.1)	53 (28.0)	39 (10.2)	<0.001	64 (19.5)	31 (18.9)	33 (20.1)	0.889
Multi-segmental EVT, n (%)	112 (19.6)	51 (27.0)	61 (16.0)	0.002	78 (23.8)	38 (23.2)	40 (24.4)	0.897
AI and FP lesions, n (%)	55 (9.6)	19 (10.1)	36 (9.4)		36 (11.0)	19 (11.6)	17 (10.4)	
FP and BK lesions, n (%)	3 (0.5)	31 (16.4)	22 (5.8)		39 (11.9)	18 (11.0)	21 (12.8)	
AI and BK lesions, n (%)	1 (0.2)	0 (0.0)	1 (0.3)		1 (0.3)	0 (0.0)	1 (0.6)	
AI, FP, and BK lesions, n (%)	3 (0.5)	1 (0.5)	2 (0.5)		2 (0.6)	1 (0.6)	1 (0.6)	
Procedural results								
BMS, n (%)	307 (53.9)	87 (46.0)	220 (57.7)	0.01	173 (52.7)	82 (50.0)	91 (55.5)	0.376
DES, n (%)	64 (11.2)	8 (4.2)	56 (14.7)	<0.001	32 (9.8)	7 (4.3)	25 (15.2)	0.001
SG, n (%)	37 (6.5)	8 (4.2)	29 (7.6)	0.149	21 (6.4)	8 (4.9)	13 (7.9)	0.367
DCB, n (%)	103 (18.1)	36 (19.0)	67 (17.6)	0.729	58 (17.7)	32 (19.5)	26 (15.9)	0.47
POBA, n (%)	191 (33.5)	89 (47.1)	102 (26.8)	<0.001	120 (36.6)	68 (41.5)	52 (31.7)	0.085
Hybrid use, n (%)	125 (21.9)	39 (20.6)	86 (22.6)	0.667	64 (19.5)	32 (19.5)	38 (23.2)	0.501

Continuous data are presented as means ± standard deviation. Categorical data are given as counts (percentage).

AI: aortoiliac; BK: below-knee; BMI: body mass index; BMS: bare metal stent; CABG: coronary artery bypass graft; CFS: Clinical Frailty Scale; CLTI: chronic limb-threatening ischemia; DAPT: dual antiplatelet therapy; DCB: drug-coated balloon; DES: drug-eluting stent; EVT: endovascular therapy; FP: femoropopliteal; LEAD: lower extremity artery disease; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; SAPT: single antiplatelet therapy; SG: stent graft



Months		0	6	12	18	24
SAPT	Number at risk	164	132	116	102	63
	%	0	6.4	9.4	11.1	14.2
DAPT	Number at risk	164	125	112	101	66
	%	0	8.7	9.5	10.3	11.3

Months		0	1	6	12	18	24
SAPT	Number at risk	164	160	137	121	104	67
	%	0	2.5	4.0	6.9	8.6	11.7
DAPT	Number at risk	164	154	132	122	106	69
	%	0	6.1	3.3	4.1	5.7	6.7

Fig. 2 Bleeding events. (**A**) The Kaplan-Meier estimate showed rates of cumulative bleeding events of 14.2% in the SAPT group and 11.3% in the DAPT group at 24 months (p = 0.775). (**B**) Landmark analysis presented that rates of cumulative bleeding events in the SAPT group and the DAPT group were 2.5% and 6.1% at 30 days (p = 0.106) and 11.7% and 6.7% at 24 months after 30 days, respectively (p = 0.162). DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy

Table 2 Details of bleeding and ischemic events

	Overall (n = 570)	SAPT (n = 189)	DAPT (n = 381)	p-Value
Bleeding events				
Bleeding with surgical repair, n (%)	10 (1.8)	5 (2.6)	5 (1.3)	0.312
Intracranial hemorrhage, n (%)	6 (1.1)	2 (1.1)	4 (1.0)	1
Gastrointestinal bleeding, n (%)	14 (2.5)	5 (2.6)	9 (2.4)	0.782
Progressive anemia, n (%)	24 (4.2)	9 (4.8)	15 (3.9)	0.661
Hemorrhagic death, n (%)	3 (0.5)	1 (0.5)	2 (0.5)	1
Ischemic events				
Acute limb ischemia, n (%)	6 (1.1)	3 (1.6)	3 (0.8)	0.404
Myocardial infarction, n (%)	5 (0.9)	3 (1.6)	2 (0.5)	0.339
Stroke, n (%)	13 (2.3)	2 (1.1)	11 (2.9)	0.237
Other ischemic events, n (%)	140 (24.6)	47 (24.9)	93 (24.4)	0.918
Ischemic death, n (%)	6 (1.1)	3 (1.6)	3 (0.8)	0.404

Categorical data are given as counts (percentage).

DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy

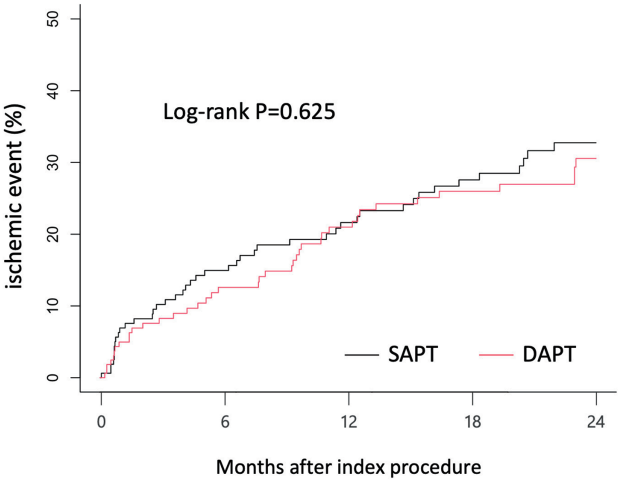
groups (p = 0.63 and p = 0.97); 28.7% and 28.4% and 40.7% and 36.8% in the non-CLTI and CLTI groups (p = 0.984 and p = 0.394); and 20.0% and 25.6%, 39.2% and 32.4%, and 33.6% and 39.0% in the AI, FP, and BK segments, respectively (p = 0.439, p = 0.268, and p = 0.964; **Fig. 5**). There were no significant differences in the bleeding or ischemic events between subgroups.

All-cause death at 24 months

The Kaplan–Meier estimate showed an all-cause death rate of 17.8% in the SAPT group and 19.3% in the DAPT group at 24 months (p = 0.777; **Supplementary Fig. 1**).

Discussion

This study presented the following three findings: (1) there was no significant difference in acute to mid-term bleeding events after EVT between SAPT and DAPT; (2) there was no significant difference in mid-term ischemic events; and (3) the above results were consistent in each subgroup according to the patient characteristics and treatment



Months		0	6	12	18	24
SAPT	Number at risk	164	123	97	80	55
	%	0	14.9	21.6	27.6	32.7
DAPT	Number at risk	164	118	99	78	53
	%	0	12.6	21.0	26.0	30.6

Fig. 3 Ischemic events. The rates of cumulative ischemic events estimated using the Kaplan-Meier method were 32.7% in the SAPT group and 30.6% in the DAPT group at 24 months. There was no significant difference between the two groups (p = 0.625). DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy

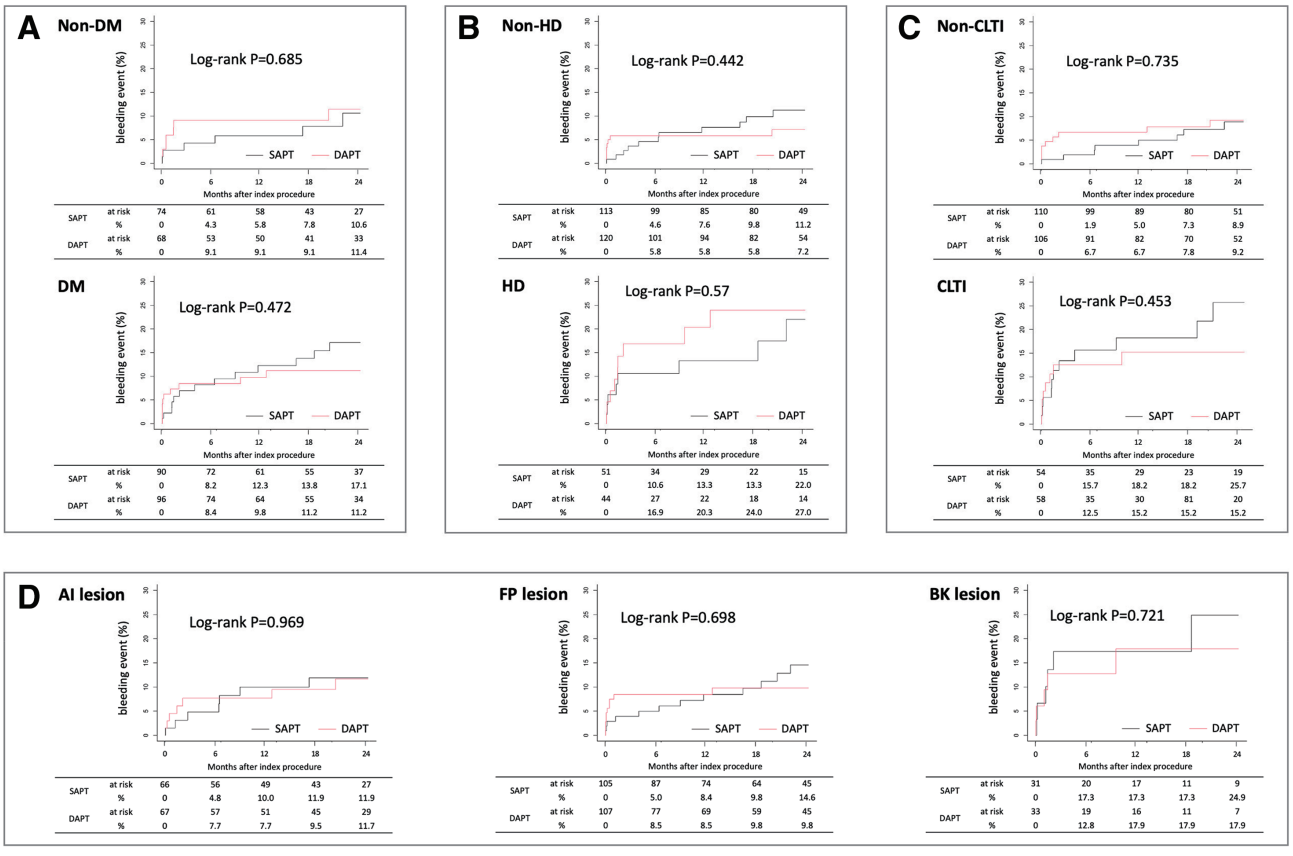


Fig. 4 Bleeding events in each subgroup. Bleeding events at 24 months between the SAPT and DAPT groups occurred at (**A**) 10.6% and 11.4% and 17.1% and 11.2% in the non-DM and DM groups, respectively (p = 0.685 and p = 0.472); (**B**) 11.2% and 7.2% and 22.0% and 27.0% in the non-HD and HD groups (p = 0.442 and p = 0.57); (**C**) 8.9% and 9.2% and 25.7% and 15.2% in the non-CLTI and CLTI groups (p = 0.735 and p = 0.453); and (**D**) 11.9% and 11.7%, 14.6% and 9.8%, and 24.9% and 17.9% in the AI, FP, and BK segments, respectively (p = 0.969, p = 0.698, and p = 0.721). There were no significant differences between the subgroups. AI: aortoiliac; BK: below-knee; CLTI: chronic limb-threatening ischemia; DAPT: dual antiplatelet therapy; DM: diabetes mellitus; FP: femoropopliteal; HD: hemodialysis; SAPT: single antiplatelet therapy

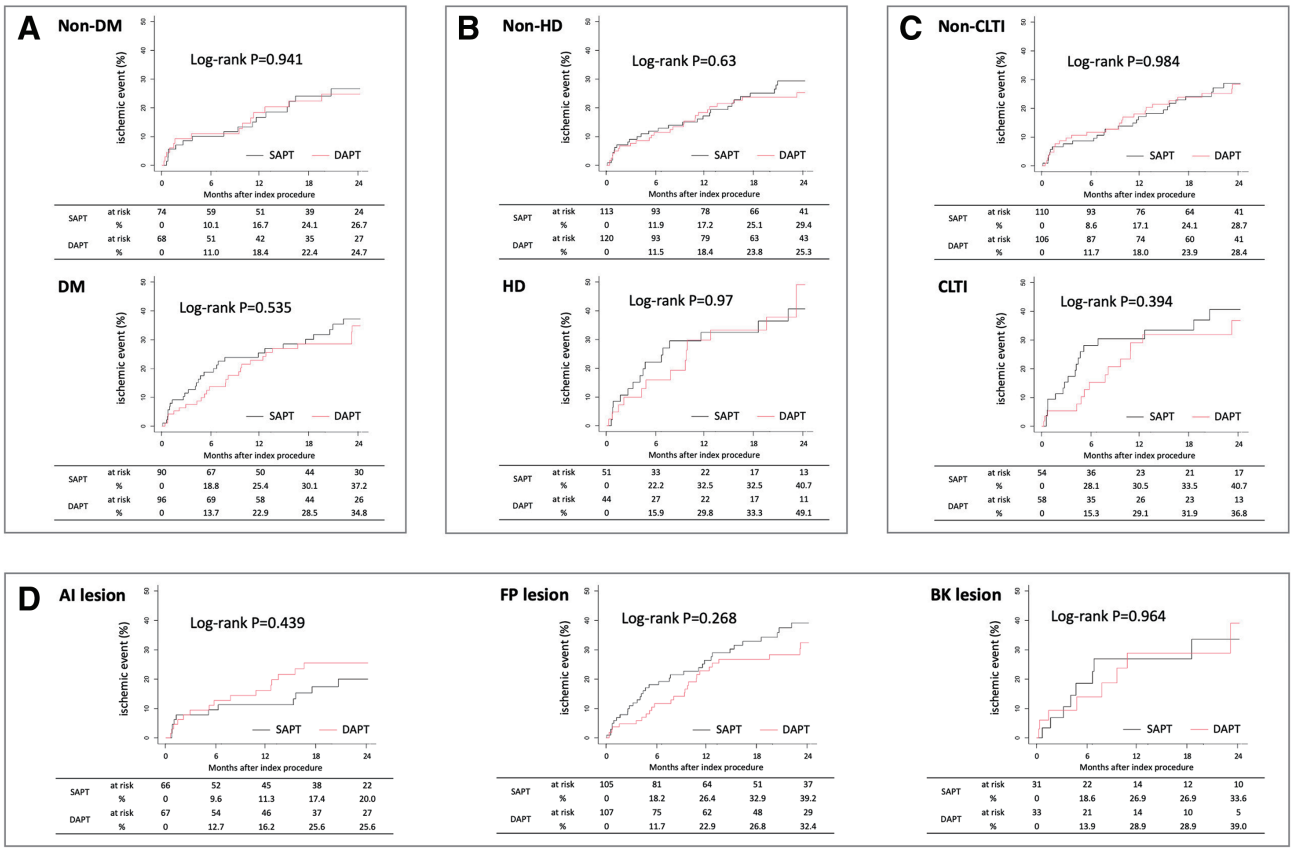


Fig. 5 Ischemic events in each subgroup. Ischemic events at 24 months between the SAPT and DAPT groups occurred at (**A**) 26.7% and 24.7% and 37.2% and 34.8% in the non-DM and DM groups, respectively (p = 0.941 and p = 0.535); (**B**) 29.4% and 25.3% and 40.7% and 49.1% in the non-HD and HD groups (p = 0.63 and p = 0.97); (**C**) 28.7% and 28.4% and 40.7% and 36.8% in the non-CLTI and CLTI groups (p = 0.984 and p = 0.394); and (**D**) 20.0% and 25.6%, 39.2% and 32.4%, and 33.6% and 39.0% in the AI, FP, and BK segments, respectively (p = 0.439, p = 0.268, and p = 0.964). There were no significant differences between the subgroups. AI: aortoiliac; BK: below-knee; CLTI: chronic limb-threatening ischemia; DAPT: dual antiplatelet therapy; DM: diabetes mellitus; FP: femoropopliteal; HD: hemodialysis; SAPT: single antiplatelet therapy

segments. To the best of our knowledge, this is the first direct comparison between SAPT and DAPT in evaluating bleeding events after EVT in patients with LEAD.

The CHARISMA trial peripheral artery disease cohort showed that DAPT in patients with LEAD reduced myocardial infarction and hospitalization for ischemic events compared with SAPT, whereas DAPT did not decrease MACE or increase minor bleeding events.[6] However, this study had several limitations, such as the inclusion of asymptomatic LEAD patients and post-hoc analysis. Subsequently, a retrospective study reported that DAPT was associated with a reduction in MACEs and all-cause mortality in 2015; however, bleeding events were not mentioned.[8] Based on the above results, the superiority of DAPT over SAPT remains unclear, and the current guidelines do not recommend routine DAPT in patients with LEAD.[12–15] In contrast, the post-EVT period is a special phase that requires more intense AT to prevent acute lower extremity events. In the guidelines, at least 1 month of DAPT was recommended after EVT, especially if stents were deployed in the FP segment, following the recommendation for coronary artery disease (CAD).[12–15] However, the evidence of DAPT in patients with LEAD after EVT is limited. The MIRROR study, which was the only RCT comparing SAPT and DAPT after EVT, reported that DAPT decreased the TLR rate at 6 months compared with SAPT, whereas the efficacy did not persist after DAPT was discontinued.[7] Furthermore, that study did not evaluate bleeding events. A recent retrospective study reported that more than 6 months of DAPT decreased MACE and major adverse limb events without increasing major bleeding events compared with SAPT or less than 6 months of DAPT.[9] However, the study did not clearly demonstrate the superiority of DAPT over SAPT in the post-EVT period because it did not directly compare SAPT and DAPT, and did not include a population of current mainstream

devices, such as polymer-coated drug-eluting stents and drug-coated balloons. In the present study, there were no significant differences in bleeding and ischemic events between the SAPT and DAPT groups, and the difference in platelet reactivity between patients with LEAD and CAD was speculated to be one of the reasons for these results. A previous study reported that LEAD patients indicate higher residual platelet reactivity in response to adenosine diphosphate and arachidonic acid than CAD patients,[18] and a recent consensus document suggested that LEAD patients may respond worse to antiplatelet agents than CAD patients.[19] Therefore, patients with LEAD may be less likely to experience bleeding events with DAPT, whereas they may be more likely to experience ischemic events. It is interesting to note that the results were consistent across subgroups by conditions known to cause high platelet reactivity, such as DM, hemodialysis, and CLTI, as well as by treatment segments with different therapeutic devices.[20–22] As a result of the present study, it is useful to know that the intensity of antiplatelet therapy can be safely increased in LEAD patients, requiring DAPT, such as the post-PCI period. Thus, future studies are required.

Limitations

This study had several limitations. First, this was a non-randomized, retrospective study. Second, the duration of DAPT was not uniform. Third, the evaluation of each EVT device was not performed. Fourth, only Japanese patients were enrolled in this study, and studies on populations of other races may show different results.

Conclusion

There were no significant differences in bleeding or ischemic events between the SAPT and DAPT groups. The results were consistent in each subgroup according to the patient characteristics and treatment segments.

Declarations

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of each institution (Ethical Committee in Central Japan International Medical Center, Approval number/2021-032). Written informed consent was obtained from each patient or their relatives prior to the index procedure.

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Disclosure statement

All authors have no conflicts of interest.

Author contributions

Study conception: TY and TT
Data collection: AK and TT
Analysis: NY, RN, and KS
Investigation: RN and NY
Manuscript preparation: TY and KS
Funding acquisition: TA and AK
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors.

Supplementary Materials

Supplementary Figure 1 All-cause death
The Kaplan–Meier estimate showed an all-cause death rate of 17.8% in the SAPT group and 19.3% in the DAPT group at 24 months. There was no significant difference between the two groups (p = 0.777). DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy

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