Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Aspirin Versus Clopidogrel as Single Antithrombotic Therapy After Transcatheter Aortic Valve Replacement

Insight From the OCEAN-TAVI Registry

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BACKGROUND: Current guidelines recommend dual antiplatelet therapy for the first 1 to 6 months after transcatheter aortic valve replacement (TAVR); however, recent studies have reported better outcomes with single antiplatelet therapy than with dual antiplatelet therapy in the occurrence of bleeding events, while not increasing thrombotic events. However, no data exist about optimal single antiplatelet therapy following TAVR.

METHODS: Patients who underwent TAVR between October 2013 and May 2017 were enrolled from the OCEAN-TAVI Japanese multicenter registry (Optimized Transcatheter Valvular Intervention). After excluding 1759 patients, 829 who received aspirin (100 mg/d) or clopidogrel (75 mg/d) after TAVR were identified and stratified according to the presence or absence of anticoagulation. Propensity score matching was performed to adjust the baseline characteristics between the aspirin and clopidogrel groups. Outcomes of interest were all-cause and cardiovascular deaths, stroke, and life-threatening or major bleeding within 2 years following TAVR.

RESULTS: After propensity score matching, 98 and 157 pairs of patients without and with anticoagulation, respectively, were identified. Falsification end points of pneumonia, urinary tract infection, and hip fracture were evaluated, and their rates were not different between groups. All-cause deaths were not statistically different between the groups in patients with (aspirin, 17.5%; clopidogrel, 11.1%; log-rank P=0.07) and without (aspirin, 29.6%; clopidogrel, 20.1%; log-rank P=0.15) anticoagulation at 2 years post-TAVR, whereas clopidogrel was associated with a lower cardiovascular mortality at 2 years in patients with (aspirin, 8.5%; clopidogrel, 2.7%; log-rank P=0.03) and without (aspirin, 18.0%; clopidogrel, 5.2%; log-rank P=0.02) anticoagulation.

CONCLUSIONS: We demonstrated that clopidogrel monotherapy was associated with a lower incidence of cardiovascular death compared with aspirin monotherapy during the 2-year follow-up after TAVR regardless of anticoagulation use.

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Key Words: myocardial infarction ■ sudden cardiac death ■ thrombosis ■ transcatheter aortic valve replacement ■ valvular heart disease

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WHAT IS KNOWN

- Transcatheter aortic valve replacement is an established therapy for patients with symptomatic severe aortic stenosis.
- Current guidelines recommend dual antiplatelet therapy following transcatheter aortic valve replacement, but optimal antithrombotic therapy has not been determined.

WHAT THE STUDY ADDS

- This study demonstrated that the incidence of cardiovascular death is lower in patients treated with clopidogrel than in patients treated with aspirin irrespective of whether they received additional anticoagulation drugs or not.
- Clopidogrel may reduce the incidence of thrombotic events and subsequent cardiovascular death following transcatheter aortic valve replacement.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
DOAC	direct oral anticoagulant
SAPT	single antiplatelet therapy
SCD	sudden cardiac death
TAVR	transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is a well-established therapy for symptomatic severe aortic stenosis in all surgical-risk subsets.[1–3] However, little is known about the optimal antithrombotic regimen following TAVR.[4]

The current guidelines recommend dual antiplatelet therapy (DAPT) for the first 1 to 6 months after TAVR followed by single antiplatelet therapy (SAPT)[5,6]; however, this recommendation is mainly based on expert consensus rather than clinical evidence. Patients who undergo TAVR are usually old, frail, and have a high risk of ischemic and bleeding events, especially Asian patients.[7–9] A meta-analysis comparing SAPT versus DAPT after TAVR showed that DAPT was associated with a higher incidence of bleeding complications and not with any reduction in ischemic events compared with SAPT.[10] These findings are not consistent with the current recommendation of DAPT following TAVR. In coronary artery, cerebrovascular, and peripheral artery diseases, clopidogrel has been reported to be potentially more effective than aspirin to obtain an optimal balance between preventing ischemic events and the risk of bleeding.[8,11,12] However, there are no studies comparing optimal SAPT following TAVR.

This study aimed to compare the clinical outcomes between aspirin and clopidogrel as SAPT in patients who undergo TAVR.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Patients

Patients who underwent TAVR for aortic stenosis from October 2013 to May 2017 were enrolled from the OCEAN-TAVI registry (Optimized Transcatheter Valvular Intervention)—a nationwide observational, multicenter study at 14 collaborating hospitals in Japan. TAVR procedures were performed according to the standards of each participating center. All study participants provided informed consent, and this registry was approved by the ethics committees of all the participating institutions. The OCEAN-TAVI registry was registered with the University Hospital Medical Information Network Clinical Trial Registry and accepted by the International Committee of Medical Journal Editors (UMIN-ID: 000020423).

Study Outcomes

Outcomes of our interest were the incidences of all-cause death, cardiovascular death, stroke, and life-threatening or major bleeding during the 2-year follow-up period. Outcomes at 30 days after TAVR were also evaluated. The outcomes were defined according to the Valve Academic Research Consortium 2 criteria.[13]

Follow-Up

We obtained clinical follow-up data at 1 month, 6 months, and 1 year for the first year and annually thereafter at the participating institutions. Additional follow-up data were collected via phone calls. The follow-up rate at 2 years was 98.4%, and the median follow-up period was 604 days (interquartile range, 377–799 days). Clinical research coordinators specifically trained in recording TAVR procedures or experienced physicians confirmed the proper recording of data. Data reported on the internet-based system were checked via self-audit by sites. Data committee members regularly audited the database for completeness and consistency.

Statistical Analysis

The baseline characteristics were compared between the aspirin and clopidogrel groups. Categorical variables are expressed as number (percentage) and continuous variables as the median (interquartile range, IQ1–IQ3). Two-sided χ^2 test or Fisher exact test (for cell count of under 10) was used for comparing categorical variables. All continuous variables were analyzed using the Mann-Whitney *U* tests.

To reduce the potential bias due to nonrandom assignment of patients, propensity scores were estimated using a logistic regression model with aspirin and clopidogrel as the categorical variables and 25 baseline covariates as predictor variables after dividing patients according to the presence or absence of anticoagulation. The full list of covariates appears in Appendix I in the Data Supplement. Greedy nearest neighbor matching was performed on the logit of the propensity score with a caliper width of 0.2× the pooled SD of the logit of the propensity scores for the cohort. The balance between covariates before

and after propensity matching was ascertained by measuring the absolute standardized mean difference. Covariates were considered adequately balanced between the two groups if the standardized mean difference was ≤0.1.

To evaluate the potential for residual confounding, we tested for the association between prescription of aspirin or clopidogrel and falsification end points of pneumonia, urinary tract infection, and hip fracture. These end points served as a negative control, as rates of pneumonia, urinary tract infection, and hip fracture are unlikely to be influenced by the choice of prescription of antiplatelets and thus should theoretically be the same in the absence of residual confounding.

To estimate the survival curves for time-to-event variables, a Kaplan-Meier curve was plotted and the log-rank test was used for comparisons between the groups. Landmark analyses were also conducted and the data displayed using a 30-day landmark period, with one set of curves for 0 to 30 days and a second from 30 to 730 days. $P<0.05$ was considered to be statistically significant. SPSS, version 26.0 (IBM Corp, Armonk, NY), and R 3.1.0 software were used for all statistical analyses.

RESULTS

We identified 2588 patients who underwent TAVR during the study period. Of these, 1759 were excluded because they received DAPT (n=1328) or SAPT other than aspirin or clopidogrel (n=78), did not receive any antiplatelet therapy (n=334), or had missing data (n=19; Figure 1). The site-level variation in choice of SAPT or DAPT, comparison of baseline characteristics, and 30-day and 2-year outcomes between patients on SAPT and DAPT are shown in Figure I in the Data Supplement and Tables I and II in the Data Supplement. Overall, 829 patients who received either aspirin (100 mg/d; n=574) or clopidogrel (75 mg/d; n=255) as SAPT were identified post-procedure. The site-level variation in use of clopidogrel and aspirin monotherapy is shown in Figure II in the Data Supplement. After stratifying patients according to the presence or absence of anticoagulation, propensity score matching was performed, and 98 and 157 pairs of patients without and with anticoagulation, respectively, were identified.

Baseline Characteristics

Before propensity score matching, there were statistically significant differences regarding the presence of comorbidities (hypertension and atrial fibrillation), approach site for TAVR, and valve type (Table 1). After propensity matching, the median age was 85 years and about 70% patients were women in both with and without anticoagulation groups. The mean Society of Thoracic Surgeons score was 5.8% (without anticoagulation) and 7.5% (with anticoagulation). In

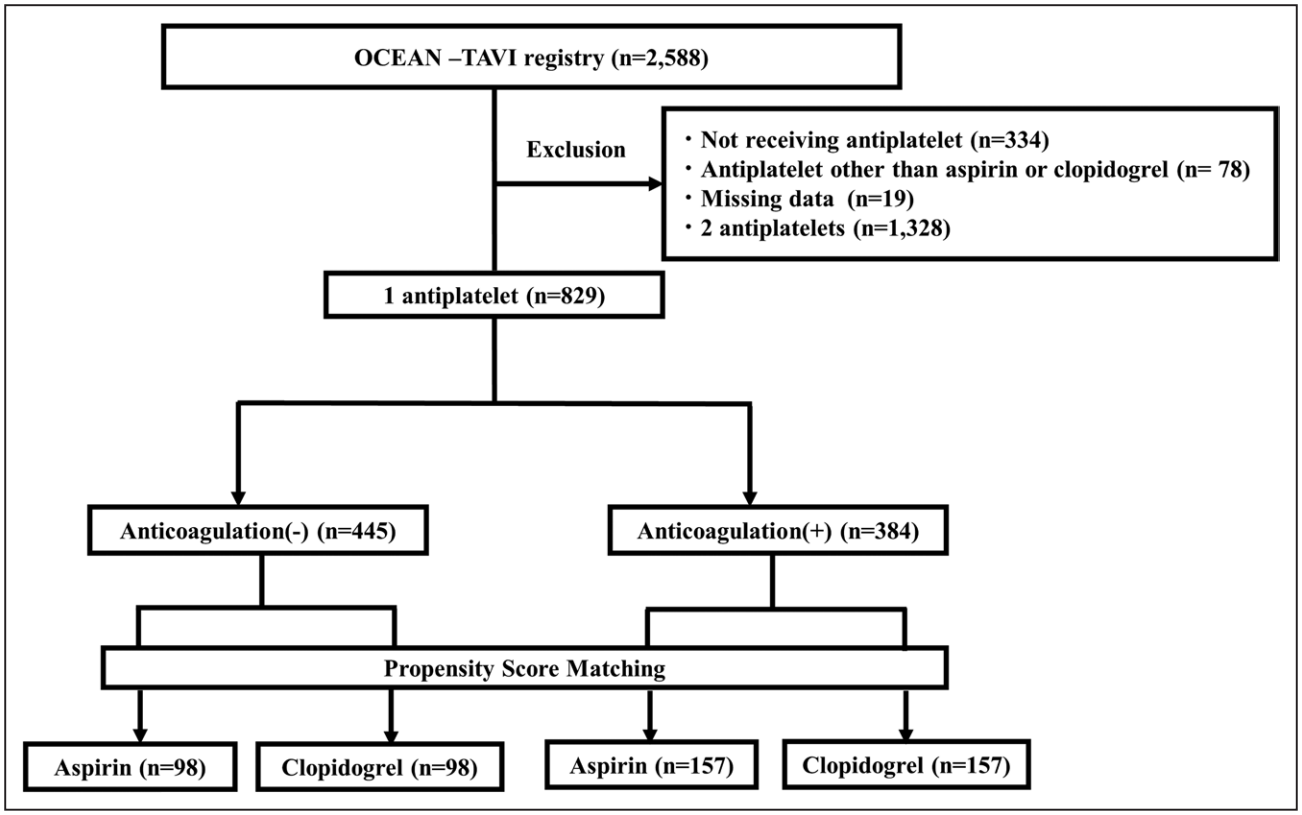

Figure 1. Flowchart of the study population.
Covariates used in the propensity score matching are shown in Appendix I in the Data Supplement. OCEAN-TAVI indicates Optimized Transcatheter Valvular Intervention.

Table 1. Baseline Characteristics of the Study Population According to Treatment Group

Characteristics	Before matching			After matching							
				No anticoagulation				Anticoagulation			
	Aspirin (n=574)	Clopidogrel (n=255)	*P* value	Aspirin (n=98)	Clopidogrel (n=98)	*P* value	SMD	Aspirin (n=157)	Clopidogrel (n=157)	*P* value	SMD
Age, y	85 (82–88)	84 (82–88)	0.32	85 (81–88)	84 (81–88)	0.68	−0.025	85 (81–88)	85.0 (81–88)	0.75	0.048
Body mass index, kg/m^2	21.8 (19.3–24.1)	21.5 (19.3–24.0)	0.62	21.9 (19.0–23.8)	21.3 (19.2–23.6)	0.91	0.002	21.8 (19.4–24.4)	21.6 (19.4–24.2)	0.57	−0.066
Men	183 (31.9)	77 (30.2)	0.63	34 (34.7)	27 (27.6)	0.28	−0.071	50 (31.8)	50 (31.8)	1.00	<0.001
Diabetes	128 (22.3)	59 (23.1)	0.79	19 (19.4)	20 (20.4)	0.86	0.010	41 (26.1)	39 (24.8)	0.80	−0.013
Hypertension	433 (75.4)	205 (80.4)	0.01	80 (81.6)	81 (82.7)	0.85	0.010	123 (78.3)	124 (79.0)	0.89	0.006
Dyslipidemia	232 (40.4)	116 (45.5)	0.17	48 (49.0)	44 (44.9)	0.57	−0.041	67 (42.7)	72 (45.9)	0.57	0.032
Coronary artery disease	189 (32.9)	83 (32.5)	0.92	24 (24.5)	24 (24.5)	1.00	<0.001	56 (35.7)	59 (37.6)	0.73	0.019
Peripheral artery disease	96 (16.7)	45 (17.6)	0.74	16 (16.3)	15 (15.3)	0.85	−0.010	28 (17.8)	30 (19.1)	0.77	0.013
Chronic kidney disease	414 (72.1)	188 (73.7)	0.84	64 (65.3)	62 (63.3)	0.77	−0.020	129 (82.2)	126 (80.3)	0.67	−0.019
NYHA 3 or 4	309 (53.8)	155 (60.8)	0.06	45 (45.9)	50 (51.0)	0.48	0.051	106 (67.5)	105 (66.9)	0.90	−0.006
Atrial fibrillation	192 (33.4)	131 (51.4)	<0.01	7 (7.1)	6 (6.1)	0.77	−0.010	124 (79.0)	125 (79.6)	0.89	0.006
Stroke	81 (14.1)	34 (13.3)	0.77	6 (6.1)	10 (10.2)	0.30	0.041	27 (17.2)	28 (17.8)	0.88	0.006
β-Blocker	217 (37.8)	91 (35.7)	0.56	26 (26.5)	25 (25.5)	0.87	−0.010	68 (43.3)	66 (42.0)	0.82	−0.013
Proton pump inhibitor	434 (75.6)	189 (74.1)	0.65	69 (70.4)	66 (67.3)	0.64	−0.031	126 (80.3)	123 (78.3)	0.68	−0.019
STS-PROM score, %	7.0 (4.7–10.4)	6.7 (4.9–9.8)	0.52	5.8 (4.3–8.7)	5.9 (4.5–8.7)	0.79	0.022	7.8 (5.4–10.7)	7.2 (5.2–10.3)	0.52	0.030
Previous CABG	49 (8.5)	13 (5.1)	0.08	6 (6.1)	3 (3.1)	0.25	−0.031	8 (5.1)	10 (6.4)	0.63	0.013
Echocardiographic variables											
PFV, m/s	4.5 (4.0–5.0)	4.4 (3.9–4.9)	0.14	4.7 (4.1–5.2)	4.6 (4.2–5.2)	0.99	0.082	4.2 (3.7–4.8)	4.3 (3.7–4.8)	0.97	0.025
Mean gradient, mm Hg	47.0 (36.0–61.0)	45.0 (36.0–58.0)	0.23	51.0 (39.9–63.9)	51.2 (40.0–61.6)	0.97	−0.003	42.0 (31.0–54.5)	42.0 (31.6–56.0)	0.98	0.006
AVA, cm^2	0.61 (0.49–0.73)	0.63 (0.50–0.77)	0.41	0.63 (0.48–0.73)	0.63 (0.48–0.78)	0.87	0.010	0.63 (0.52–0.74)	0.63 (0.50–0.77)	0.86	0.006
Indexed AVA, cm^2/m^2	0.43 (0.35–0.50)	0.43 (0.34–0.51)	0.63	0.45 (0.34–0.54)	0.43 (0.35–0.54)	0.69	−0.020	0.44 (0.36–0.52)	0.44 (0.34–0.53)	0.99	−0.006
Ejection fraction, %	63.3 (53.7–69.2)	63.3 (51.4–68.1)	0.34	63.0 (56.0–69.1)	65.0 (57.5–70.7)	0.49	0.048	60.7 (48.4–66.7)	60.0 (50.0–65.0)	0.31	0.015
Aortic regurgitation			0.49			0.30	−0.041			1.00	<0.001
None-mild	518 (90.2)	234 (91.7)		88 (89.8)	92 (93.9)			142 (90.4)	142 (90.4)		
Moderate/ severe	56 (9.7)	21 (8.2)		10 (10.2)	6 (6.1)			15 (9.6)	15 (9.6)		
Procedural characteristics											
TF approach	445 (77.5)	216 (84.7)	0.02	82 (83.7)	83 (84.7)	0.85	0.010	132 (84.1)	133 (84.7)	0.88	0.006
Valve type			<0.01			0.62	−0.031			0.28	0.057
SAPIEN XT	309 (53.8)	114 (44.7)		46 (46.9)	40 (40.8)			88 (56.1)	74 (47.1)		
SAPIEN 3	190 (33.1)	89 (34.9)		31 (31.6)	39 (39.8)			46 (29.3)	50 (31.8)		
Corevalve	38 (6.6)	37 (14.5)		19 (19.4)	16 (16.3)			12 (7.6)	21 (13.4)		
EvolutR	37 (6.4)	15 (5.9)		2 (2.0)	3 (3.1)			11 (7.0)	12 (7.6)		
Local anesthesia	171 (29.8)	61 (23.9)	0.08	35 (35.7)	35 (35.7)	1.00	<0.001	28 (17.8)	26 (16.6)	0.77	−0.013

Values are median (interquartile range, IQ1–IQ3) or n (%). AVA indicates aortic valve area; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; PFV, peak flow velocity; SMD, standardized mean difference; and STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

the matched cohort, baseline characteristics were well balanced, and the standardized mean differences were all <0.1. There was no significant difference between the groups in terms of the procedural characteristics and postprocedural hemodynamics evaluated by echocardiography (Table 2).

Two-Year Outcomes

All-cause deaths were not statistically different between the groups in patients with (aspirin, 17.5%; clopidogrel, 11.1%; log-rank *P*=0.07) and without (aspirin, 29.6%; clopidogrel, 20.1%; log-rank *P*=0.15) anticoagulation at 2 years after TAVR (Figures 2A and 3A), whereas clopidogrel was associated with a lower cardiovascular mortality at 2 years in patients with (aspirin, 8.5%; clopidogrel, 2.7%; log-rank *P*=0.03) and without (aspirin, 18.0%; clopidogrel, 5.2%; log-rank *P*=0.02) anticoagulation (Figures 2B and 3B).

There was no significant difference at 2 years in the incidence of life-threatening or major bleeding and that of stroke between the aspirin and clopidogrel groups (Figures 2C, 2D, 3C, and 3D). Landmark analyses for all-cause death or stroke after 30 days post-TAVR showed consistent results (Figures III and IV in the Data Supplement).

The reasons of the cardiovascular deaths during the 2-year follow-up are shown in Table 3. There were statistically significant differences in the incidence of sudden cardiac death (SCD; without anticoagulation, *P*=0.01; with anticoagulation, *P*=0.03) between the groups.

The falsification end points of pneumonia, urinary tract infection, and hip fracture demonstrated no statistically significant differences between aspirin and clopidogrel (Table III in the Data Supplement).

Thirty-Day Outcomes

The 30-day outcomes are shown in Table 4. The mortality rate was 1.0% with no difference between the groups without anticoagulation (1.0% versus 1.0%; *P*=1.00) and 0.6% with no difference between the groups with anticoagulation (1.3% versus 0.0%; *P*=0.16). There were no differences between the groups in the incidence of stroke within 30 days post-procedure.

Subgroup Analysis

The prescription rate of warfarin or direct oral anticoagulant (DOAC) by the type of antiplatelet agent is demonstrated in Table IV in the Data Supplement. The incidence of life-threatening or major bleeding at 2 years was numerically higher in patients on warfarin compared with those on DOAC, but it did not reach statistical difference ([aspirin] warfarin, 22.7%; DOAC, 13.5%; *P*=0.10; [clopidogrel] warfarin, 25.3%; DOAC, 13.6%; *P*=0.08). The all-cause death rate at 2 years was higher in the warfarin group than in the DOAC group in patients on aspirin (warfarin, 28.0%; DOAC, 5.5%; *P*=0.002), while it was not different in patients on clopidogrel (warfarin, 9.8%; DOAC, 12.8%; *P*=0.70; Table V in the Data Supplement).

DISCUSSION

The main findings of this study are that aspirin was associated with an increased incidence of cardiovascular death than clopidogrel during the midterm follow-up after TAVR regardless of anticoagulation use in the propensity-matched cohort. However, the cumulative incidence of all-cause death was not statistically different in these groups.

Table 2. Procedural Characteristics of the Study Population

	No anticoagulation			Anticoagulation		
	Aspirin (n=98)	Clopidogrel (n=98)	*P* value	Aspirin (n=157)	Clopidogrel (n=157)	*P* value
Procedural characteristics						
Device success	94 (95.9)	93 (94.9)	0.73	147 (93.6)	144 (91.7)	0.52
Predilatation	57 (58.2)	68 (69.4)	0.10	93 (59.2)	83 (52.9)	0.26
Need for second valve	1 (1.0)	0 (0.0)	0.32*	1 (0.6)	2 (1.3)	0.56*
Conversion to open surgery	0 (0.0)	2 (2.0)	0.16*	2 (1.3)	1 (0.6)	0.56*
All vascular complications	13 (13.3)	16 (16.3)	0.55	15 (9.6)	13 (8.3)	0.69
Echocardiography						
THVmax, m/s	2.2 (1.8–2.7)	2.3 (2.0–2.5)	0.91	2.1 (1.8–2.4)	2.1 (1.8–2.4)	0.91
Mean gradient, mm Hg	10.6 (7.2–14.5)	10.4 (8.0–13.0)	0.87	9.0 (7.0–12.0)	9.0 (7.0–12.0)	0.79
Indexed EOA, cm^2/m^2	1.18 (0.98–1.41)	1.20 (1.00–1.33)	0.93	1.13 (1.00–1.29)	1.10 (0.94–1.31)	0.42
Aortic regurgitation			0.56*			0.76*
None-mild	97 (99.0)	96 (98.0)		151 (96.2)	152 (96.8)	
Moderate/severe	1 (1.0)	2 (2.0)		6 (3.8)	5 (3.2)	

Values are median (interquartile range, IQ1–IQ3) or n (%). EOA indicates effective orifice area; and THV, transcatheter heart valve.
*Fisher exact test.

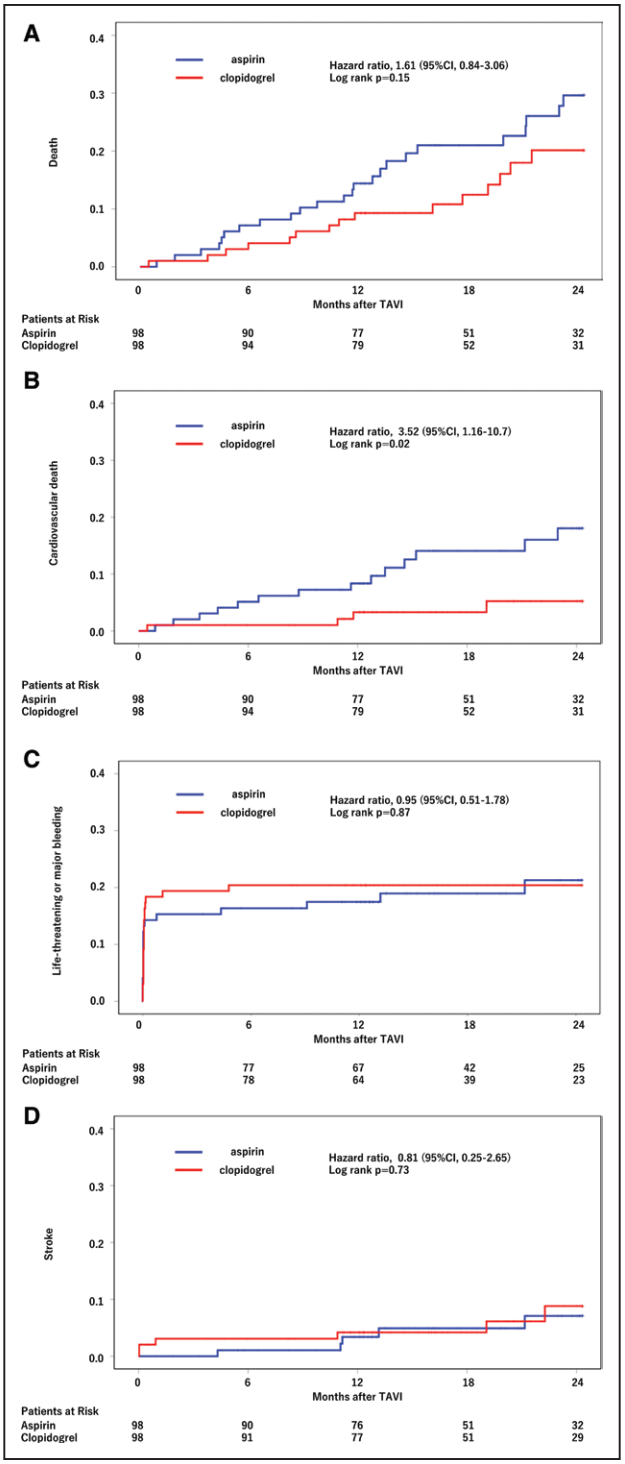

Figure 2. Kaplan-Meier curves of the primary outcomes in patients without anticoagulation.
Death (**A**), cardiovascular death (**B**), life-threatening or major bleeding (**C**), and stroke (**D**). TAVI indicates transcatheter aortic valve implantation.

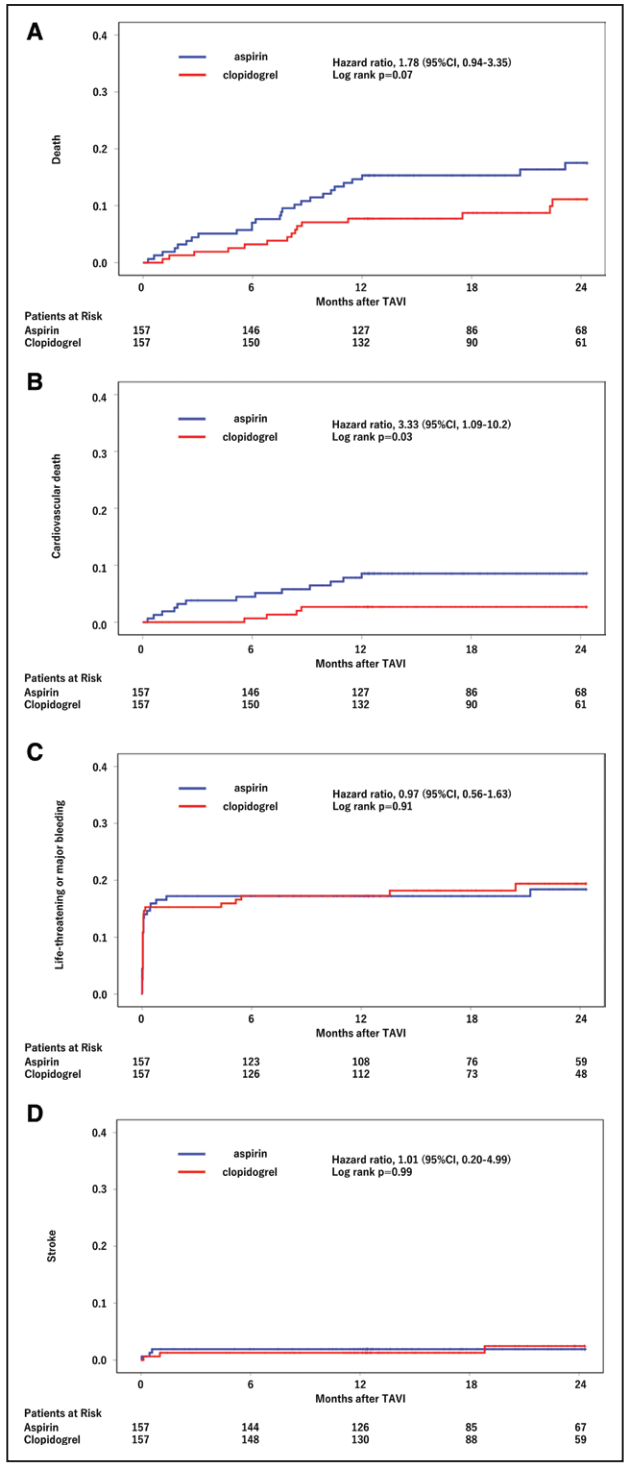

Figure 3. Kaplan-Meier curves of the primary outcomes in patients with anticoagulation.
Death (**A**), cardiovascular death (**B**), life-threatening or major bleeding (**C**), and stroke (**D**). TAVI indicates transcatheter aortic valve implantation.

The current guidelines recommend DAPT for the first 1 to 6 months followed by SAPT after TAVR[5,6]; however, this recommendation is mainly based on clinical trials in the field of percutaneous coronary intervention and on expert consensus. Additionally, no data exist on whether antiplatelet or anticoagulation therapy is the preferred choice of treatment.

Recent observational and randomized trials comparing DAPT with SAPT after TAVR, such as the POPular TAVI trial (Antiplatelet Therapy for Patients Undergoing

Table 3. Reasons for Cardiovascular Death in Each Group

	No anticoagulation			Anticoagulation		
Death reason	Aspirin (n=98)	Clopidogrel (n=98)	*P* value*	Aspirin (n=157)	Clopidogrel (n=157)	*P* value*
Heart failure	2	2	0.70	3	3	0.66
Hemorrhagic stroke	1	2	0.50	1	0	0.50
Ischemic stroke	3	0	0.12	3	0	0.12
Infectious endocarditis	2	0	0.25	1	1	0.75
Sudden cardiac death	6	0	0.01	5	0	0.03

Values are n (%).
*Fisher exact test.

Transcatheter Aortic Valve Implantation),[14] showed that DAPT was associated with a higher rate of major adverse events post-TAVR, mainly increased risk of major bleeding, whereas there was no decrease in the incidence of ischemic events.[10,14–17] Furthermore, the GALLILEO trials (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) showed that the groups that received anticoagulants had higher rates of death or thromboembolic complications and bleeding events.[18] Patients who undergo TAVR are usually old, frail, and have a high risk of both ischemic and bleeding events; hence, it is important to know which antiplatelet therapy should be recommended in such patients.

In this study, clopidogrel was associated with a lower incidence of cardiovascular death after TAVR, presumably due to a lower rate of thromboembolic events, such as ischemic stroke or SCD at the midterm follow-up, but not with increasing the incidence of bleeding events (Table 3).

Maurizio et al[12] demonstrated lower risks of major adverse cardiovascular or cerebrovascular events, recurrent stroke, and bleeding events with clopidogrel than with aspirin. In patients with increased risk for cardiovascular events, clopidogrel was reportedly more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death.[11,19,20] The proportion of all SCDs resulting from myocardial infarction or coronary artery disease remains up to 80%.[21,22] These are the possible reasons why clopidogrel reduced the incidence of stroke and myocardial infarction and subsequent SCD in our study. However, 4 of 5 strokes in patients without anticoagulation and 3 of 4 strokes in patients with anticoagulation in this study occurred within 24 hours post-procedure. At least 50% of the strokes within 30 days post-TAVR are reported to occur within 24 hours post-procedure and seem related mainly to embolic complications from procedure-related mechanical interaction between the valvular system and the aorta or aortic valves,[23,24] and the role of antithrombotics in the prevention of ischemic stroke in a short period is limited.

This study has several limitations. First, this was not a randomized study; therefore, despite performing a propensity score matching for statistical adjustment in the baseline characteristics, the influence of unidentified confounders was unavoidable. Some factors, such as recent bleeding or thrombotic events or recent percutaneous coronary intervention, may affect the choice of antiplatelet therapy, but we could not consider these factors. Additionally, there was also site-level variation in antiplatelet use. To overcome this concern, we performed falsification end point analysis that suggested no significant residual confounding. Second, almost all our patients were Japanese, whose genetic polymorphisms, such as CYP2C19 allele,[25] and clopidogrel metabolism are reported to be different from those in the Western population. Some studies that evaluated the platelet activity post-TAVR showed a high platelet reactivity against clopidogrel in a significant number of patients[26–28]; however, genetic polymorphisms were not taken into account in our study. Third, the number of patients and events in this study were relatively small because patients who

Table 4. Thirty-Day Outcomes in Each Group

	No anticoagulation			Anticoagulation		
	Aspirin (n=98)	Clopidogrel (n=98)	*P* value	Aspirin (n=157)	Clopidogrel (n=157)	*P* value
Death	1 (1.0)	1 (1.0)	1.00*	2 (1.3)	0 (0.0)	0.16*
Cardiovascular death	1 (1.0)	1 (1.0)	1.00*	2 (1.3)	0 (0.0)	0.16*
Life-threatening/major bleeding	18 (18.4)	14 (14.3)	0.44	26 (16.6)	24 (15.3)	0.76
Gastrointestinal bleeding	2 (2.0)	0 (0.0)	0.16*	0 (0.0)	0 (0.0)	NA
Stroke	2 (2.0)	3 (3.1)	0.65*	3 (1.9)	1 (0.6)	0.31*
≤24 h	1 (1.0)	3 (3.1)		2 (1.3)	1 (0.6)	

Values are n (%). NA indicates not applicable.
*Fisher exact test.

were on the current guideline-recommended DAPT were excluded. In our dataset, patients on SAPT were more likely to have higher bleeding risks than those on DAPT; therefore, our findings may not be applicable for patients with lower bleeding risks. However, the POPular TAVI trial[14] demonstrated better outcomes with SAPT than with DAPT, in terms of bleeding or thromboembolism regardless of bleeding risks, supporting the generalizability of our study. Future randomized controlled trials with a larger number of patients with equal bleeding profiles are warranted to validate our findings. Fourth, change in medication during the follow-up period was not considered in our analysis. Tables VI and VII in the Data Supplement show the data of antithrombotic regimen at 1 year. In about 30% of patients without anticoagulation and 40% of those with anticoagulation, the antithrombotic regimen was changed during the 1-year follow-up. Importantly, the pattern of the change in antithrombotic regimen was similar between groups. Considering only discharge medication is analogous to intention-to-treat analysis in clinical trials, which is an accepted methodology for the comparison of drug effectiveness. Finally, we did not consider the occurrence of leaflet thrombosis that may affect the clinical outcome. However, Yanagisawa et al[29] reported that subclinical leaflet thrombosis did not affect the cumulative event rates of death, stroke, and rehospitalization for heart failure. The valve performance post-TAVR was not statistically different between the groups (Figure V in the Data Supplement). The incidence of increased mean aortic valve gradients post-TAVR suggesting valve deterioration was similar between the groups in our study.

CONCLUSIONS

Our data demonstrated that clopidogrel was associated with lower incidences of cardiovascular deaths after TAVR regardless of anticoagulation use, possibly due to a lower rate of stroke and SCD at midterm follow-up. As the indication for TAVR is expanding, these results can help in deciding the optimal antithrombotic therapy after TAVR.

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Disclosures

Drs. Yamamoto, Tada, Naganuma, Shirai, Mizutani, Tabata, Ueno, and Watanabe are clinical proctors for Edwards Lifesciences and Medtronic. Drs. Takagi and Hayashida are clinical proctors for Edwards Lifesciences. The other authors report no conflicts.

Supplemental Materials

Appendix I
Figures I–V
Tables I–VII

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