Additional Effects of Antiplatelet Therapy on Anticoagulant Agents in Patients With Bioprosthetic Valves and Atrial Fibrillation

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Background: The additional effects of single-antiplatelet therapy (SAPT) on anticoagulant therapy are still unclear in patients with atrial fibrillation (AF) after bioprosthetic valve replacement.

Methods and Results: We conducted a subanalysis of a multicenter, retrospective, observational registry of patients with bioprosthetic valves and AF in Japan. Patients administered anticoagulants alone comprised the ACA group (n=107), and patients given concomitant SAPT and anticoagulant therapy comprised the On SAPT group (n=82). The primary efficacy endpoint was the incidence of stroke/systemic embolism, and the primary safety endpoint was the incidence of major bleeding. The observation period was 46.3±24.6 months. The primary efficacy endpoint occurred in 12 patients, and the cumulative incidence of primary efficacy events was significantly higher in the ACA group compared with the On SAPT group (P=0.039). The primary safety endpoint occurred in 22 patients, and the cumulative incidence of primary safety events was similar between groups (P=0.66). No differences between the groups were observed for cardiac events.

Conclusions: Additional SAPT on anticoagulant therapy in patients with bioprosthetic valves and AF was associated with a reduction in stroke/systemic embolic events, although the cumulative incidence of bleeding was similar, regardless of additional SAPT. These findings suggest that additional SAPT on anticoagulant therapy may be safe and effective in real-world clinical settings.

Key Words: Anticoagulant therapy; Antiplatelet agents; Atrial fibrillation; Bioprosthetic valves; Embolism

The number of patients with bioprosthetic valves, especially the aortic valve, has increased substantially over the past 2 decades.^{1,2} The main advantage of bioprosthetic valves over mechanical valves is the avoidance of long-term anticoagulant therapy. On the other hand, atrial fibrillation (AF) has also increased with the aging demographic.³ As a result, patients with bioprosthetic valves and AF need to be treated with oral anticoagulants to prevent embolic stroke, even though avoiding oral anticoagulants is the main benefit of implanting bioprosthetic valves.⁴

In current guidelines for valvular heart disease,⁵⁻⁷ bioprosthetic valve replacement is recommended for patients over 65 years of age in the aortic valve and 70 years of age in the mitral valve. Therefore, patients with bioprosthetic valves and AF are frequently elderly and have a high prevalence of chronic coronary artery disease (CAD).^{8,9} Additionally,

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tionally, in patients with bioprosthetic valves, the presence of CAD is associated with a higher risk of late death.⁸ Although oral anticoagulants are more effective than antiplatelet agents in preventing embolic stroke in patients with AF, antiplatelet agents may be more protective in reducing vascular events in patients with CAD.^{10,11} As a result, many patients with bioprosthetic valves and AF are treated with a single antiplatelet agent and anticoagulant therapy.

A subanalysis of the ENGAGE AF-TIMI 48 trial in patients with AF¹² identified that patients receiving an antiplatelet agent on anticoagulant therapy had a similar risk of stroke or systemic embolic events and a higher rate of bleeding compared with those not receiving an anti-

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	All (n=189)	ACA group (n=107)	On SAPT group (n=82)	P value
Male	93 (49.2)	59 (55.1)	34 (41.5)	0.062
Age (years), mean±SD	76.8±5.8	77.0±5.6	76.5±6.1	0.52
Weight (kg), mean±SD	53.1±10.4	53.3±11.1	52.8±9.4	0.77
BMI (kg/m²), mean±SD	21.7±3.6	21.4±3.5	22.0±3.7	0.27
CHADS₂ score				
Mean±SD	2.4±1.2	2.4±1.3	2.3±1.2	0.97
≥2.0	142 (75.5)	78 (73.6)	64 (78.1)	0.48
CHA₂DS₂-VASc score				
Mean±SD	3.9±1.4	3.9±1.4	4.0±1.4	0.67
≥3.0	161 (85.6)	90 (84.9)	71 (86.6)	0.74
HAS-BLED score				
Mean±SD	3.6±1.2	3.1±1.3	4.0±1.0	<0.001
≥3.0	83 (79.8)	31 (64.6)	52 (92.9)	<0.001
eGFR (mL/min/1.73 m²), mean±SD	55.0±18.8	56.2±18.3	53.4±19.4	0.32
Ccr (mL/min)				
Median (IQR)	45.2 (36.5–58.6)	47.4 (38.6–59.1)	44.3 (35.9–57.3)	0.33
<30	23 (14.4)	12 (13.0)	11 (16.2)	0.52
≥30, <50	70 (43.8)	38 (41.3)	32 (47.1)	
≥50	67 (41.9)	42 (45.7)	25 (36.8)	
Observation period (months), mean±SD	46.3±24.6	44.8±24.8	48.3±24.3	0.33
Type of AF				0.034
Paroxysmal	31 (16.4)	16 (15.0)	15 (18.3)	
Persistent	63 (33.3)	44 (41.1)	19 (23.2)	
Permanent	95 (50.3)	47 (43.9)	48 (58.5)	
History of cardiovascular disease				
Ischemic stroke	31 (16.4)	20 (18.7)	11 (13.4)	0.33
Hemorrhagic stroke	4 (2.1)	3 (2.8)	1 (1.2)	0.45
Intracranial hemorrhage	7 (3.7)	7 (6.5)	0 (0.0)	0.018
Systemic embolism	2 (1.1)	1 (0.9)	1 (1.2)	0.85
Major bleeding	7 (3.7)	5 (4.7)	2 (2.4)	0.42
Comorbidities				
Hypertension	136 (72.0)	75 (70.1)	61 (74.4)	0.51
Dyslipidemia	84 (44.4)	43 (40.2)	41 (50.0)	0.18
Diabetes mellitus	51 (27.0)	30 (28.0)	21 (25.6)	0.71
Hyperuricemia	26 (13.8)	17 (15.9)	9 (11.0)	0.33
Heart failure	80 (42.3)	39 (36.5)	41 (50.0)	0.062
LV systolic dysfunction	31 (16.4)	19 (17.8)	12 (14.6)	0.57
Myocardial infarction	7 (3.7)	2 (1.9)	5 (6.1)	0.13
Peripheral arterial disease	9 (4.8)	5 (4.7)	4 (4.9)	0.95
Aortic plaque	2 (1.1)	1 (0.9)	1 (1.2)	0.85
Renal dysfunction	5 (2.7)	1 (0.9)	4 (4.9)	0.094
Liver dysfunction	1 (0.5)	0 (0.0)	1 (1.2)	0.25
Chronic respiratory disease	26 (13.8)	18 (16.8)	8 (9.8)	0.16
Thrombosis and embolism	1 (0.5)	0 (0.0)	1 (1.2)	0.25
Malignant tumor	22 (11.6)	14 (13.1)	8 (9.8)	0.48
Dementia	5 (2.7)	3 (2.8)	2 (2.4)	0.88
Digestive diseases	25 (13.2)	12 (11.2)	13 (15.9)	0.35
LVEF				
<40%	20 (14.2)	15 (17.7)	5 (8.9)	0.34
40–49%	9 (6.4)	5 (5.9)	4 (7.1)	
≥50%	112 (79.4)	65 (76.5)	47 (83.9)	

Data are presented as n (%) unless otherwise specified. ACA, anticoagulant therapy alone; AF, atrial fibrillation; BMI, body mass index; Ccr, creatinine clearance; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LV, left ventricular; LVEF, LV ejection fraction; On SAPT, single-antiplatelet therapy with anticoagulant therapy; SD, standard deviation.

	All (n=189)	ACA group (n=107)	On SAPT group (n=82)	P value
Concomitant Maze procedure	35 (18.5)	15 (14.0)	20 (24.4)	0.069
Prosthesis position				
Aortic valve	82 (43.4)	43 (40.2)	39 (47.6)	0.054
Mitral valve	66 (34.9)	34 (31.8)	32 (39.0)	
Both valve	41 (21.7)	30 (28.0)	11 (13.4)	
Aortic valve (n=123)				
VHD subtype				
Stenosis	81 (65.9)	52 (71.2)	29 (58.0)	0.28
Regurgitation	37 (30.1)	19 (26.0)	18 (36.0)	
Both	5 (4.1)	2 (2.7)	3 (6.0)	
Operation type				
Surgery	113 (91.9)	66 (90.4)	47 (94.0)	0.47
TAVI	10 (8.1)	7 (9.6)	3 (6.0)	
History of replacement				
First replacement	114 (92.7)	66 (90.4)	48 (96.0)	0.24
Re-replacement	9 (7.3)	7 (9.6)	2 (4.0)	
Mitral valve (n=107)				
VHD subtype				
Stenosis	53 (50.0)	35 (55.6)	18 (41.9)	0.36
Regurgitation	47 (44.3)	25 (39.7)	22 (51.2)	
Both	6 (5.7)	3 (4.8)	3 (7.0)	
History of replacement				
First replacement	94 (87.9)	58 (90.6)	36 (83.7)	0.28
Re-replacement	13 (12.2)	6 (9.4)	7 (16.3)	

Data are presented as n (%). TAVI, transcatheter aortic valve implantation; VHD, valvular heart disease. Other abbreviations as in Table 1.

platelet agent. However, in patients with bioprosthetic valves and AF, the additional effects of a single antiplatelet agent on anticoagulant therapy are still unclear. Therefore, the aim of this study was to compare the efficacy and safety of antiplatelet therapy on anticoagulant therapy in patients with bioprosthetic valves and AF.

Methods

Study Population

The study design and primary results of the BioProsthetic Valves with Atrial Fibrillation (BPV-AF) Study have been previously reported.¹³ In brief, it was a retrospective, multicenter, observational registry that enrolled 214 patients with bioprosthetic valves and AF in Japan between March 2011 and March 2018. The study inclusion criteria were: (1) at least 3 months since bioprosthetic valve replacement; (2) definitive diagnosis of AF; and (3) clinical examination data could be collected for at least 6 months after satisfying criteria 1 and 2. The key exclusion criteria were participation in interventional studies during the data collection period and mechanical valve replacement.

The study patients were subdivided into those receiving anticoagulant therapy alone (ACA group, n=107) and those receiving concomitant single-antiplatelet therapy (SAPT) on anticoagulant therapy (On SAPT group, n=82). Patients with no anticoagulant therapy (n=22) or anticoagulant and dual-antiplatelet therapy (n=3) were excluded. Baseline characteristics and long-term clinical outcomes were compared between groups. The efficacy and safety of SAPT on

anticoagulant therapy were evaluated.

The main study was classified as non-interventional without invasive procedures or human-derived specimens; thus, acquisition of informed consent from each patient was unnecessary. However, the details of the study were disseminated to patients and their families/caregivers, with the opportunity for patients to decline study participation (opt-out). The study was conducted in compliance with all applicable local and national regulations (Declaration of Helsinki). The ethical committee at each study site approved the study protocol prior to registry commencement (M30-044-3).

Study Endpoints and Definitions

The primary efficacy endpoint was the incidence of stroke or systemic embolism during the observation period. The primary safety endpoint was the incidence of major bleeding events during the observation period, based on International Society of Thrombosis and Hemostasis (ISTH) criteria.¹⁴ The secondary endpoint included cardiac events (heart failure requiring hospitalization, re-replacement of the bioprosthetic valve, and myocardial infarction) and bleeding events (major, clinically relevant, and minor bleeding).

Measurements

The details of obtaining baseline measurements are given in the main paper.¹³ Data for changes in the antithrombotic regimen and occurrence of major surgery and events were collected every 6 months. Laboratory test values were also collected every 6±3 months, and echocardiographic

Table 3. Administration Status of Warfarin				
	All (n=189)	ACA group (n=107)	On SAPT group (n=82)	P value
No. being treated	174 (92.1)	97 (90.7)	77 (93.9)	0.41
TTR				
Mean $\pm$ SD	54.1 $\pm$ 37.4	59.1 $\pm$ 38.2	50.8 $\pm$ 36.8	0.26
Median (IQR)	55.5 (24.1–98.9)	64.2 (26.8–100.0)	53.9 (15.3–91.1)	0.22
PT-INR				
<1.6	51 (34.9)	26 (34.7)	25 (35.2)	0.62
1.6–2.6	80 (54.8)	43 (57.3)	37 (52.1)	
>2.6	15 (10.3)	6 (8.0)	9 (12.7)	

Data are presented as n (%) unless otherwise specified. PT-INR, prothrombin time to international normalized ratio; TTR, time in therapeutic range. Other abbreviations as in Table 1.

Primary efficacy outcome

Figure 1. Kaplan-Meier curves of the primary efficacy outcome show the cumulative incidence of stroke or systemic embolism during the observational period. ACA, anticoagulant therapy alone; On SAPT, single-antiplatelet therapy with anticoagulant therapy.

data were collected annually.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), depending on the distribution of data, and were compared using Student's t-test or the Kruskal-Wallis test. Categorical variables are presented as percentages and were compared using the χ^2 test or Fisher's test. Incidence proportion and incidence rates in percent and per 100 person-years (PY) were calculated for all endpoints during the observation period. The cumulative incidence rates of the endpoints in each group were evaluated using Kaplan-Meier methods. The Cox proportional hazards method was used to estimate the hazard ratio (HR) of ACA to On SAPT. To reduce the effect of treatment selection bias and potential confounding, we performed rigorous adjustment for significant differences in the characteristics of patients using weighted Cox proportional hazards regression models using inverse-

probability-of-treatment weighting (IPTW). With that technique, weights for ACA patients were the inverse of the propensity score, and weights for On SAPT patients were the inverse of (1-propensity score). The propensity score was estimated by multiple logistic regression model, with the treatment, age, sex, AF, previous history of intracranial hemorrhage and heart failure, and estimated glomerular filtration rate. The level of significance was set as $P < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline and Operative Characteristics

Baseline characteristics, including previous history of cardiovascular disease, comorbidities, and left ventricular function, are described in **Table 1**. The observation period was 46.3 $\pm$ 24.6 months for the entire population, 44.8 $\pm$ 24.8 months in the ACA group, and 48.3 $\pm$ 24.3 months in the

Table 4. Incident Rates of Events in Patients With Paroxysmal or Persistent and Permanent AF

	ACA group (n=16)	On SAPT group (n=15)	P value
Paroxysmal AF (n=31)			
Efficacy events	0	0	NA
Safety events	0	3	0.10
Bleeding events	1	8	0.006
Persistent or permanent AF (n=158)	(n=91)	(n=67)	
Efficacy events	10	2	0.061
Safety events	11	8	0.98
Bleeding events	23	14	0.52

NA, not applicable. Other abbreviations as in Table 1.

Primary safety outcome

	No. at risk							
On SAPT group	82	80	66	56	49	39	23	14
ACA group	107	98	86	67	49	39	27	17

Figure 2. Kaplan-Meier curves of the primary safety outcome show the cumulative incidence of major bleeding events during the observational period. ACA, anticoagulant therapy alone; On SAPT, single-antiplatelet therapy with anticoagulant therapy.

On SAPT group ($P=0.33$). In total, 49.2% of patients were male, and the percentage of male patients was slightly higher in the ACA group compared with the On SAPT group. The mean age of patients was 76.8 ± 5.8 years, and the average CHA₂DS₂-VASc score was 3.9 ± 1.4 . The HAS-BLED score was significantly lower in the ACA group compared with the On SAPT group (3.1 ± 1.3 vs. 4.0 ± 1.0 , $P<0.001$). Regarding the type of AF, the percentage of patients with paroxysmal AF was similar between groups (ACA group: 15.0% vs. On SAPT group: 18.3%; $P=0.54$). A history of intracranial hemorrhage was more frequent in the ACA group compared with the On SAPT group (ACA group: 6.5% vs. On SAPT group: 0%; $P=0.018$), but there were no differences for other baseline characteristics.

The operative characteristics are shown in **Table 2**. There were no significant differences between groups for prosthesis position. In both the aortic and mitral valves, the subtype of disease (stenosis, regurgitation, or both) was also similar. Regarding the characteristics of the aortic valve, the percentage of patients undergoing transcatheter aortic valve implantation (TAVI) was similarly low (<10%) in

both groups. Concomitant Maze procedure was performed in 35 patients (18.5%), and there were no significant differences between the groups (ACA group: 14.0% vs. On SAPT group: 24.4%; $P=0.069$).

Administration Status of Anticoagulant Agents

The administration status of anticoagulant agents is described in **Table 3**. The percentage of patients treated with direct oral anticoagulants (DOACs) was low (<10%) in both groups, and no difference was observed between the groups. In warfarin-treated patients, the mean time in the therapeutic range (TTR) was 59.1% in the ACA group and 50.8% in the On SAPT group ($P=0.26$). The prothrombin time to international normalized ratio (PT-INR) was also similar between the groups.

Primary Efficacy Endpoints: ACA vs. On SAPT

The primary efficacy endpoint (stroke/systemic embolism) occurred in 12 patients (10 [2.67/100 PY] in the ACA group and 2 [0.61/100 PY] in the On SAPT group) during the observation period. The Kaplan-Meier curve showed that

the cumulative incidence of primary efficacy events was significantly higher in the ACA group compared with the On SAPT group (log-rank test, $P=0.039$; **Figure 1**). Compared with the On SAPT group, the unadjusted HR (95% confidence interval [CI]) for primary efficacy events in the ACA group was 4.34 (0.95 to 19.84) ($P=0.058$), and the IPTW-adjusted HR (95% CI) was 5.01 (1.02 to 24.55) ($P=0.047$). In patients with primary efficacy events, those who underwent TAVI were not included, and the prosthesis positions were as follows: ACA group: aortic valve in 5, mitral valve in 2, and both valves in 3; On SAPT group: mitral valve in 1 and both valves in 1. No primary efficacy events occurred in patients with paroxysmal AF (**Table 4**). Concomitant Maze procedure did not affect the incidence rate of primary efficacy events (1 [2.9%] of 35 patients with concomitant Maze procedure and 11 [7.1%] of 154 patients without concomitant Maze procedure, $P=0.70$).

Safety Endpoints: ACA vs. On SAPT

The primary safety endpoint (major bleeding) occurred in 22 patients (11 [2.94/100 PY] in the ACA group and 11 [3.51/100 PY] in the On SAPT group) during the observation period. The Kaplan-Meier curve showed that the cumulative incidence of primary safety events was similar between groups (log-rank test, $P=0.66$; **Figure 2**). In patients with primary safety events, those who underwent TAVI were not included, and the prosthesis positions were as follows: ACA group: aortic valve in 2, mitral valve in 7, and both valves in 2; On SAPT group: aortic valve in 3, mitral valve in 6, and both valves in 2.

Of all 189 patients, the incidence rate of primary safety events was similar between patients with paroxysmal AF and those with persistent or permanent AF (3 [9.7%] of 31 patients with paroxysmal AF and 19 [12.0%] of 158 patients with persistent or permanent AF, $P=1.00$). However, all 3 patients with primary safety endpoints and paroxysmal AF were in the On SAPT group (**Table 4**). Concomitant Maze procedure did not affect the incidence rate of primary

safety events (3 [8.6%] of 35 patients with concomitant Maze procedure and 19 [12.3%] of 154 patients without concomitant Maze procedure, $P=0.77$).

Bleeding events (major, clinically relevant, and minor bleeding) occurred in 46 patients (24 [7.16/100 PY] in the ACA group and 22 [7.54/100PY] in the On SAPT group) during the observation period. In the Kaplan-Meier curve, the cumulative incidence of bleeding events was comparable between groups (log-rank test, $P=0.79$; **Figure 3A**). Of the 9 patients with bleeding events and paroxysmal AF, 8 (89%) were in the On SAPT group, and 14 (38%) of 37 patients with bleeding events and persistent or permanent AF were in the On SAPT group (**Table 4**).

Prevalence of Cardiac Events: ACA vs. On SAPT

The baseline and follow-up data of laboratory tests and echocardiography are shown in **Table 5**. Regarding prosthetic valve function, the percentages of significant acceleration in peak velocity in the aortic valve (≥ 3.0 m/s) and mitral valve (≥ 2.0 m/s) were similar between the ACA and On SAPT groups during the observation period (aortic valve: 14.9% vs. 24.5%, $P=0.19$; mitral valve: 62.9% vs. 65.8%, $P=0.77$). The percentages of patients with at least moderate aortic or mitral regurgitation were also comparable between the ACA and On SAPT groups (aortic regurgitation: 2.9% vs. 2.0%, $P=0.76$; mitral regurgitation: 7.9% vs. 2.6%, $P=0.26$). Any other parameters, including tricuspid regurgitation pressure gradient, hemoglobin concentration, and B-type natriuretic peptide concentration, were comparable between groups. In total, cardiac events (heart failure requiring hospitalization, re-replacement of the bioprosthetic valve, and myocardial infarction) occurred in 43 patients (22 [6.74/100 PY] in the ACA group and 21 [7.51/100 PY] in the On SAPT group) during the observation period. The Kaplan-Meier curve showed that the cumulative incidence of cardiac events was similar between groups (log-rank test, $P=0.63$; **Figure 3B**).

Table 5. Baseline and Follow-up Data of Laboratory Tests and Echocardiography

	All (n=189)	ACA group (n=107)	On SAPT group (n=82)	P value
Prosthesis position				
Aortic valve	n=123	n=73	n=50	
AVpV ≥ 3.0 m/s (during follow-up*), n (%)	22 (19.0)	10 (14.9)	12 (24.5)	0.19
AR $\geq$ moderate (during follow-up*), n (%)	3 (2.6)	2 (2.9)	1 (2.0)	0.76
Mitral valve	n=107	n=64	n=43	
E wave ≥ 2.0 m/s (during follow-up*), n (%)	64 (64.0)	39 (62.9)	25 (65.8)	0.77
MR $\geq$ moderate (during follow-up*), n (%)	6 (5.9)	5 (7.9)	1 (2.6)	0.26
Baseline laboratory and echocardiographic data				
Hemoglobin, g/dL, mean $\pm$ SD	11.7 $\pm$ 1.5	11.8 $\pm$ 1.6	11.7 $\pm$ 1.5	0.70
BNP, pg/mL, median (IQR)	141.5 (76.1–270.3)	133.7 (66.2–228.5)	159.9 (102.9–305.7)	0.11
Blood urea nitrogen, mg/dL, mean $\pm$ SD	22.1 $\pm$ 9.6	21.8 $\pm$ 9.3	22.6 $\pm$ 10.1	0.57
Creatinine, mg/dL, mean $\pm$ SD	1.0 $\pm$ 0.5	1.0 $\pm$ 0.3	1.1 $\pm$ 0.7	0.30
Total bilirubin, mg/dL, mean $\pm$ SD	0.6 $\pm$ 0.3	0.6 $\pm$ 0.2	0.6 $\pm$ 0.3	0.33
LV diastolic diameter, mm, mean $\pm$ SD	45.9 $\pm$ 9.8	46.5 $\pm$ 10.2	44.8 $\pm$ 9.0	0.32
LV systolic diameter, mm, mean $\pm$ SD	32.1 $\pm$ 9.4	33.0 $\pm$ 10.0	30.6 $\pm$ 8.3	0.15
LVEF, %, mean $\pm$ SD	56.3 $\pm$ 12.8	54.5 $\pm$ 12.5	59.1 $\pm$ 12.8	0.034
TRPG, mmHg, mean $\pm$ SD	27.3 $\pm$ 8.3	26.6 $\pm$ 7.5	28.3 $\pm$ 9.4	0.28
TR ≥ 2 , n (%)	12 (6.4)	7 (6.5)	5 (6.1)	0.90
Follow-up laboratory and echocardiographic data (during follow-up*)				
Minimum hemoglobin, g/dL, mean $\pm$ SD	10.7 $\pm$ 1.8	10.8 $\pm$ 1.7	10.6 $\pm$ 2.0	0.44
<10 g/dL, n (%)	56 (32.6)	27 (28.4)	29 (37.7)	0.20
Maximum BNP, pg/mL, median (IQR)	164 (92.6–345.3)	144.5 (90.9–341.1)	188.4 (94.7–351.2)	0.55
>200 pg/dL, n (%)	62 (43.4)	34 (42.5)	28 (44.4)	0.82
Maximum creatinine, mg/dL, mean $\pm$ SD	1.3 $\pm$ 1.0	1.3 $\pm$ 0.8	1.4 $\pm$ 1.2	0.46
Maximum total bilirubin, mg/dL, mean $\pm$ SD	0.9 $\pm$ 0.4	0.9 $\pm$ 0.4	0.8 $\pm$ 0.3	0.017
Minimum LVEF, %, mean $\pm$ SD	55.0 $\pm$ 11.3	54.0 $\pm$ 11.1	56.2 $\pm$ 11.6	0.20
<50%, n (%)	43 (24.0)	24 (23.5)	19 (24.7)	0.86
Maximum TRPG, mmHg, mean $\pm$ SD	32.1 $\pm$ 10.6	31.2 $\pm$ 11.1	33.4 $\pm$ 9.8	0.19
>40 mmHg, n (%)	33 (19.3)	18 (18.4)	15 (20.6)	0.72
TR ≥ 2 , n (%)	29 (15.3)	18 (16.8)	11 (13.4)	0.52

Data are presented as n (%) unless otherwise specified. *Regarding follow-up data, the maximum or minimum value during the follow-up period was adopted. AR, aortic regurgitation; AVpV, aortic valve peak velocity; BNP, B-type natriuretic peptide; MR, mitral regurgitation; TR, tricuspid regurgitation; TRPG, TR pressure gradient. Other abbreviations as in Table 1.

Discussion

We evaluated the clinical outcomes of patients with bioprosthetic valves and AF, and compared these outcomes between patients receiving anticoagulant therapy alone and those receiving SAPT on anticoagulant therapy. Our main findings can be summarized as follows: (1) adding SAPT on anticoagulant therapy was associated with reduced efficacy events (stroke/systemic embolism) compared with anticoagulant therapy alone; (2) the cumulative incidence of safety events (major bleeding) and bleeding events were comparable between the 2 groups; and (3) adding SAPT on anticoagulant therapy did not affect the occurrence of cardiac events during the observation period.

Additional Effects of Antiplatelet Therapy on Anticoagulant Agents for Efficacy Outcomes

In the present study, adding SAPT on anticoagulant therapy in patients with bioprosthetic valves and AF reduced stroke or systemic embolic events. In the ACA group, the cumulative incidence of efficacy outcomes at 3 years after starting the observation was around 10%, and this percentage

was similar to the warfarin-treated population within the bioprosthetic valve subgroup in the ENGAGE AF-TIMI 48 study.¹⁵ Therefore, antiplatelet therapy has an additive effect in reducing efficacy events in patients with bioprosthetic valves and AF. The subanalysis of the ENGAGE AF-TIMI 48 trial¹² identified that patients receiving antiplatelet agent on anticoagulant therapy achieved no additional benefit in terms of reducing stroke or systemic embolic events, which was different from our results. There are several possible reasons for this contradiction. First, ethnic differences may have affected the results, because Japanese individuals (or Asian individuals more generally) have lower rates of thromboembolism and more bleeding events compared with Western individuals.^{16–18} In the ENGAGE AF-TIMI 48 study, the proportion of patients enrolled from the Asia-Pacific and South Africa regions was only 16%.¹⁹ Second, the TTR of warfarin in the present study was 54.1%, which was lower than the value of 68.4% in the ENGAGE AF-TIMI 48 study.¹⁹ More than 30% of patients in both groups showed an inadequate level of PT-INR <1.6, which might affect the low level of TTR. This low TTR in real-world clinical settings may reduce

efficacy events without increasing safety outcomes by adding SAPT on anticoagulant therapy. Moreover, there is a possibility that the clinical backgrounds may be different between patients after bioprosthetic valve replacement and those with lone AF. The cumulative incidence of stroke/systemic embolism in the present study or in the warfarin-treated population subgroup in the ENGAGE AF-TIMI 48 study was higher compared with the ENGAGE AF-TIMI 48 study.^{15,19} A high incidence of stroke/systemic embolism after bioprosthetic valve replacement compared with non-valvular AF patients has been shown previously,^{20,21} and only a small number of patients with bioprosthetic valves were included in the ENGAGE AF-TIMI 48 study.¹⁹ In the Japanese population, the CHADS₂ score in the present study (2.4 ± 1.2) was higher compared with patients with non-valvular AF in the J-RHYTHM Registry 2 (1.7 ± 1.2).²⁰ A greater number of background factors for thromboembolism in patients with bioprosthetic valves and AF is related to a higher incidence of stroke/systemic embolism. Recently, subclinical leaflet thrombosis detected by computed tomography has been reported,²² which is associated with increased rates of transient ischemic attack and stroke.^{21,23} Hence, bioprosthetic valve thrombosis may also be related to an increased risk of stroke or systemic embolic events in patients with bioprosthetic valves.²⁴

Regarding pharmacological mechanisms, aspirin inhibits thromboxane A₂ formation, and clopidogrel and prasugrel inhibit the P2Y₁₂ (ADP) receptor, resulting in inhibition of different receptors on platelets. Oral anticoagulants prevent the function of various clotting factors such as factors II, VII, IX, and X and protein C and S.²⁵ Both drugs play a vital role in the treatment and prevention of embolic events, especially in stroke. The adhesion, activation, and aggregation of platelets is a main mechanism of thrombus formation in a damaged blood vessel, so antiplatelet therapy has strong clinical evidence supporting its use to prevent non-cardioembolic stroke.^{25,26} On the other hand, the interaction of vitamin K-dependent enzymes and non-enzyme cofactors leads to the formation of thrombin (factor IIa), which further amplifies the coagulation system. This system is offset by a set of anticoagulant mechanisms, and anticoagulants are strongly recommended for prevention of most types of cardioembolic stroke.^{25,26} As a result, the combination of antiplatelet therapy and anticoagulant agents might be effective for reducing efficacy events.

Additional Effects of Antiplatelet Therapy on Anticoagulant Agents for Safety Outcomes

Regarding safety outcomes, the cumulative incidence of major bleeding was lower, even in the On SAPT group of the present study (3.33/100 PY), compared with previous studies.^{15,27} Previous studies described that a TTR $\geq 75\%$ was the desired threshold to maximize effectiveness and safety, and a TTR $\geq 60\%$ was the minimum threshold to demonstrate benefit from warfarin over aspirin in patients with AF.^{28,29} However, in previous retrospective studies, the TTR of warfarin for AF patients in real-world clinical settings was often $<60\%$.^{30,31} Therefore, the low TTR in each group of the present retrospective study (59.1% in the ACA group and 50.8% in the On SAPT group) compared with the ENGAGE AF-TIMI 48 study subgroup (68.9%) may affect the low incidence of major bleeding or bleeding events.¹⁵ The cumulative incidence of bleeding events was

similar between the ACA group and the On SAPT group, although the HAS-BLED score was significantly higher in the On SAPT group compared with the On ACA group; thus, additional antiplatelet therapy on anticoagulant therapy may not increase the risk of bleeding events in Japanese clinical situations. However, limited in patients with paroxysmal AF, most bleeding events occurred in the On SAPT group, although embolic events did not occur. Therefore, additional antiplatelet therapy for patients with paroxysmal AF may tend to induce any bleeding without additional effect for reducing embolic events compared with patients on anticoagulant therapy alone. In the present study, a small number of patients received DOACs. The TTRs in the respective matched warfarin cohorts were as follows: 68.5% (apixaban), 71.0% (dabigatran), 69.7% (rivaroxaban), and 70.0% (edoxaban).^{32,33} Therefore, further studies need to be performed to confirm the additional effects of SAPT when used with DOACs.

Antithrombotic Therapy for Cardiac Events

Our results showed that concomitant antiplatelet agent use did not alter the effects of anticoagulant agents on cardiac events. On echocardiography, bioprosthetic valve dysfunction is diagnosed from an acceleration in peak velocity due to leaflet immobility or at least moderate regurgitation caused by bioprosthetic thrombosis or degeneration. No differences were observed between the ACA and On SAPT groups in terms of the percentage of patients with a peak aortic valve velocity ≥ 3.0 m/s or a peak mitral inflow velocity ≥ 2.0 m/s and those with at least moderate aortic or mitral regurgitation during the observation period. Indeed, structural deterioration due to bioprosthetic valve thrombosis is not uncommon and can occur several years after surgery.²⁴ Small bioprosthetic valve thrombi affects thrombotic events, and leaflet immobility and bioprosthetic valve dysfunction develop due to diffuse valve thrombosis. Anticoagulant therapy for AF may inhibit diffuse valve thrombosis; therefore, adding SAPT on anticoagulant therapy did not affect the occurrence of cardiac events.

Study Limitations

The main limitations of this study are the retrospective observational design and the relatively small sample size. Patients were recruited from only 3 major cardiovascular centers. Therefore, the results may not represent the current practice of the whole country. Second, the number of patients receiving DOACs was very small. Moreover, a small number of patients who underwent TAVI were included. The background characteristics of patients with TAVI were different from those with surgical bioprosthetic valve replacement in terms of antithrombotic therapy.³⁴ We have no data regarding the reasons why the additional antiplatelet therapy was administered in the On SAPT group. A possible reason may be previous percutaneous coronary intervention, but we have no data for it. Considering the retrospective nature of this registry and the absence of some background data, we could not exclude inherent bias, particularly selection bias in the comparison between the ACA and On SAPT groups. Therefore, prospective studies analyzing nationwide Japanese data with a large sample size and differences between warfarin and DOACs or surgical and transcatheter bioprosthetic valves are warranted. A large-scale prospective study (UMIN000034485) in AF patients with bioprosthetic valves is currently in progress.³⁵

Conclusions

Additional SAPT on anticoagulant therapy in patients with bioprosthetic valves and AF was associated with a reduction in stroke or systemic embolic events, but the cumulative incidence of bleeding was similar, regardless of additional SAPT on anticoagulant therapy. These findings suggest that additional SAPT on anticoagulant therapy may be effective and safe in real-world clinical settings.

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Disclosures

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Institutional Review Board Information

The ethical committee at each study site approved the study protocol prior to registry commencement (National Cerebral and Cardiovascular Center: M30-044-3)

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