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The impact of antiplatelet therapy on patients with vasospastic angina: A multicenter registry study of the Japanese Coronary Spasm Association

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ABSTRACT

Background: Antiplatelet therapy (APT) is generally used in patients with coronary artery disease. However, for patients with vasospastic angina (VSA), the impact of APT is not fully understood.
Methods: In a multicenter registry study of the Japanese Coronary Spasm Association (n = 1429), patients with or without APT were compared. The primary endpoint was major adverse cardiac events (MACEs), defined as cardiac death, non-fatal myocardial infarction, unstable angina, heart failure and appropriate ICD (Implantable cardioverter defibrillator) shock. Propensity score matching and a multivariable cox proportional hazard model were used to adjust for selection bias for treatment and potential confounding factors.
Results: In the whole population, 669 patients received APT, while 760 patients did not receive APT. Patients with APT had a greater prevalence of comorbidities, such as hypertension, diabetes, dyslipidemia and smoking, than those without APT. The prevalences of previous myocardial infarction, spontaneous ST changes, significant organic stenosis and medications including calcium channel blocker, nitrate, statin and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker were greater in patients with APT than those without APT. After propensity matching (n = 335 for both groups), during the median follow-up period of 32 months, the incidence rate of MACE was comparable between the patients with and without APT (P = 0.24). MACEs occurred in 5.7% of patients with APT and in 3.6% of those without APT (P = 0.20). All-cause death occurred in 0.6% of patients with APT and 1.8% of those without APT (p = 0.16).
Conclusion: In this multicenter registry study, anti-platelet therapy exerted no beneficial effects for VSA patients.

1. Introduction

Coronary spasm is an important mechanism of myocardial ischemia which involves acute and chronic coronary syndrome [1]. Although multiple medications have been tried, calcium channel blocker is the only class 1 drug to prevent attack of vasospastic angina (VSA) [2]. Anti-platelet therapy (APT) is an established medical treatment for overall coronary artery disease [3–4] that

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may help prevent thrombus formation following persistent coronary spasm in patients with VSA. However, its efficacy in these patients remains unclear. The present study investigated the impact of anti-platelet therapy on patients with VSA.

2. Methods

The Japanese Coronary Spasm Association was founded in 2006 and comprises 81 institutes in Japan [5–8]. The institutional review boards and/or ethics committees of all participating institutes approved the study protocol.

2.1. Study population

Enrollment of the VSA patients was made between April 1, 2003, and December 31, 2008. The subjects were registered between September 1, 2007, and December 31, 2008 [5–8]. The patient and clinical characteristics were submitted to a central database system. Follow-up data were obtained from the records of each participating or cooperating hospital and patients' regular visits to physicians in the outpatient clinic during the follow-up period. The data were collected retrospectively for patients before September 2007 and prospectively from December 31, 2008 [5–8].

VSA was diagnosed based on the spasm provocation tests and/or spontaneous angina attack based on the Guidelines for Diagnosis [2]. In brief, a positive diagnosis in the provocation test was determined when total or subtotal (>90%) coronary artery narrowing was induced under pharmacological (acetylcholine or ergnovine) or non-pharmacological (hyperventilation) challenge coronary angiography, accompanied by chest pain and/or ischemic electrocardiography (ECG) changes. Spontaneous attack of VSA was defined as angina at rest and/or on effort, accompanied by a transient ST-segment elevation or depression of>0.1 mV or a new appearance of negative U-wave on ECG, in the absence of organic coronary stenosis. Significant organic coronary stenosis is defined as angiographic stenosis > 50%.

2.2. Medical treatments

Medical treatments for VSA were selected at the discretion of each attending physician. Anti-platelet therapy included low-dose aspirin and P2Y12 inhibitors.

3. Endpoints

The primary endpoint was major adverse cardiac events (MACEs), which include cardiac death, nonfatal myocardial infarction, hospitalization due to unstable angina pectoris, heart failure, and appropriate ICD (Implantable cardioverter defibrillator) shock during the follow-up period. The secondary endpoint was all-cause mortality. Cardiac death was defined as sudden death (ie, death occurring unexpectedly without any apparent symptoms or within one hour of symptom onset or non-witnessed death in the absence of any other possible cause) or death associated with acute myocardial infarction. Acute myocardial infarction was defined in patients with prolonged (30 min) chest pain, associated with ST-segment changes and elevated levels of cardiac enzymes. Unstable angina pectoris was defined if chest discomfort or pain became recurrent or worsening along with ischemic ECG changes. Heart failure was defined if a patient showed signs of exertional dyspnea, orthopnea, rales in more than one-third of the lung fields, elevated jugular venous pressure, or pulmonary congestion on chest radiography related to cardiac dysfunction.

3.1. Statistical analyses

Categorical data were expressed as numbers (percentages), and comparison of groups were performed by Fisher's exact test. Continuous data were expressed as medians and interquartile ranges, and comparisons of group were performed with the Mann-Whitney test. Baseline characteristics of the study population were adjusted using propensity score matching. The Kaplan-Meier method was used to show the survival from MACEs and death. The log-rank test was selected for survival curves. For the subgroup analysis, the interactions between anti-platelet therapy and predefined clinical subgroups in their effects on MACEs and death were assessed by the Cox model with interaction terms.

The SPSS 21 software program (IBM Corp, Armonk, NY, USA) and R version 3.0.3 (R Foundation for statistical Computing, Vienna, Austria) were used for statistical analyses. P-values < 0.05 were considered statistically significant.

4. Results

A total of 1528 patients were registered from 47 participating hospitals. Of those, 99 patients were excluded because they did not meet the inclusion criteria. In the end, 1429 VSA patients were

Table 1
Patients' Characteristics and Treatments.

	Entire population			Matched population		
	With APT (n = 669)	Without APT (n = 760)	p-value	With APT (n = 335)	Without APT (n = 335)	p-value
Male, n (%)	540 (80.7%)	550 (72.4%)	<0.01	247 (73.7%)	253 (75.5%)	0.66
Age, years	66.07 ± 9.52	64.12 ± 11.38	<0.01	65.41 ± 9.88	66.67 ± 10.25	0.07
Hypertension, n (%)	359 (53.7%)	307 (40.4%)	<0.01	158 (47.2%)	166 (49.6%)	0.59
Diabetes, n (%)	140 (20.9%)	93 (12.2%)	<0.01	56 (16.7%)	56 (16.7%)	1.00
Dyslipidemia, n (%)	329 (49.2%)	318 (41.8%)	<0.01	156 (46.6%)	142 (42.4%)	0.31
Smoking, n (%)	419 (62.6%)	429 (56.4%)	0.02	202 (60.3%)	202 (60.3%)	1.00
Family history, n (%)	78 (11.7%)	90 (11.8%)	0.94	47 (14.0%)	37 (11.0%)	0.29
Previous MI, n (%)	77 (11.5%)	14 (1.8%)	<0.01	9 (2.7%)	13 (3.9%)	0.52
Multivessel spasm, n (%)	161 (24.1%)	213 (28%)	0.09	86 (25.7%)	90 (26.9%)	0.79
ST changes, n (%)	145 (21.7%)	127 (16.7%)	0.02	70 (20.9%)	63 (18.8%)	0.56
Organic stenosis, n (%)	172 (25.7%)	29 (3.8%)	<0.01	24 (7.2%)	19 (5.7%)	0.53
OHCA, n (%)	16 (2.4%)	19 (2.5%)	1.00	8 (2.4%)	8 (2.4%)	1.00
Ca channel blocker, n (%)	633 (94.6%)	698 (91.8%)	0.05	316 (94.3%)	313 (93.4%)	0.75
Nitrate, n (%)	355 (53.1%)	340 (44.7%)	<0.01	172 (51.3%)	166 (49.6%)	0.70
Statin, n (%)	311 (46.5%)	158 (20.8%)	<0.01	103 (30.7%)	95 (28.4%)	0.55
ACE or ARB, n (%)	218 (32.6%)	122 (16.1%)	<0.01	73 (21.8%)	71 (21.2%)	0.93

APT, anti-platelet therapy; MI, myocardial infarction; OHCA, out of hospital cardiac arrest; ACE, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2
MACE.

	Entire population			Matched population		
	With APT (n = 669)	Without APT (n = 760)	*P*-value	With APT (n = 335)	Without APT (n = 335)	*P*-value
MACEs, n (%)	47 (7.0)	38 (5.0)	0.11	19 (5.7)	12 (3.6)	0.20
Cardiac death	3 (0.4)	3 (0.4)	0.87	2 (0.6)	0 (0.0)	0.16
Non-fatal MI	6 (0.9)	3 (0.4)	0.23	1 (0.3)	2 (0.6)	0.56
Unstable angina	38 (5.7)	30 (3.9)	0.13	16 (4.8)	9 (2.7)	0.15
Heart failure	2 (0.3)	3 (0.3)	0.90	1 (0.3)	1 (0.3)	1.00
Appropriate ICD shock	0 (0)	2 (0.3)	0.18	0 (0.0)	0 (0.0)	–
All-cause death, n (%)	5 (0.7)	14 (1.8)	0.07	2 (0.6)	6 (1.8)	0.16

MACE, major adverse cardiac events; APT, anti-platelet therapy;
MI, myocardial infarction; ICD, implantable cardioverter defibrillator.

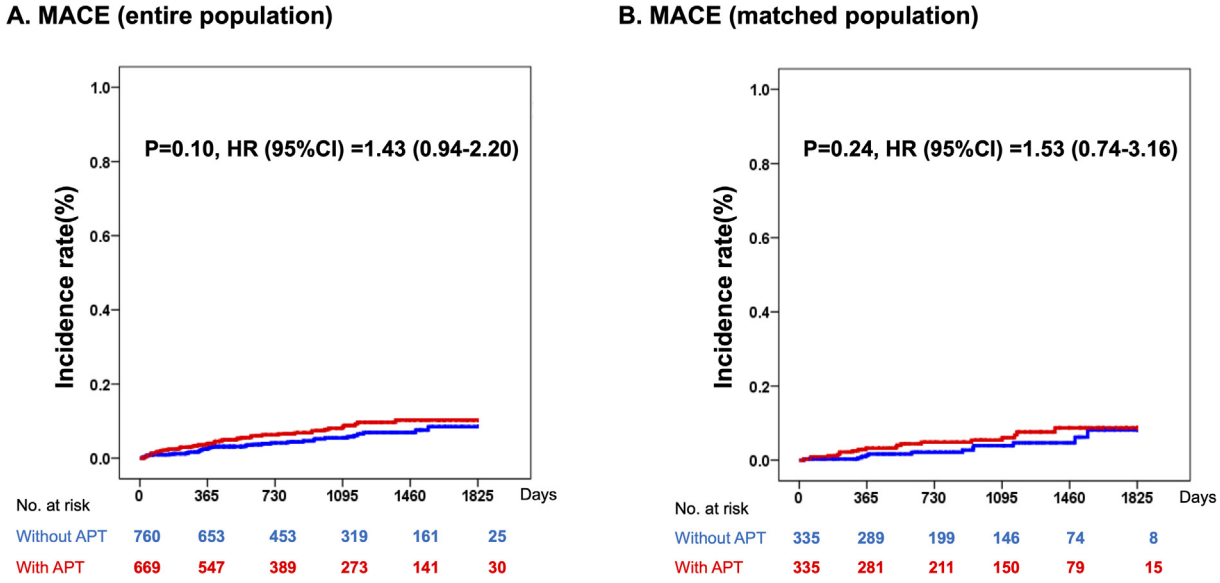

Fig. 1. Kaplan-Meier curve showing major cardiac adverse events (MACEs) in the whole population (**A**) and matched-population (**B**). APT = antiplatelet therapy, HR = hazard ratio.

analyzed, which included retrospective (n = 1276) and prospective populations (n = 153). The median follow-up period was 32 months (interquartile range: 17 to 46 months).

Antiplatelet therapy was used in 669 patients (47%) and not used in 760 patients (53%). Table 1 shows the patients' characteristics and treatment in each group for the whole population as well as the matched population. The patients who received antiplatelet therapy were characterized by significantly more risk factors than those without antiplatelet therapy, such as an older age, male gender and the presence of hypertension, diabetes, dyslipidemia and smoking. Accordingly, the prevalences of previous myocardial infarction, spontaneous ST changes and significant organic stenosis were significantly greater in the patients with antiplatelet therapy than in those without it. Therefore, the usage of all medications, including calcium channel blockers, nitrates, statins and ACE/ARB, was significantly greater in patients with antiplatelet therapy than in those without it.

By performing propensity score matching for the entire population, 329 matched pairs of patients were identified. The area under the curve of the receiver operating characteristics curve was equal to 0.767, and the Hosmer-Lemeshow test provided a P-value of 0.66, suggesting goodness of fit for the model. No significant differences were observed in the patient characteristics or treatments.

Table 2 shows the primary and secondary outcomes in VSA patients with and without anti-platelet therapy. The cumulative incidences of MACEs and all-cause death in VSA patients with and without antiplatelet therapy are shown with Kaplan-Meier curves (Fig. 1). Overall, the cumulative incidence of MACEs was numerically greater in patients with antiplatelet therapy than in those without it, although there was almost no difference after propensity score matching (Fig. 1**A and 1B**). MACEs were mainly driven by unstable angina for both groups (Table 2). Fig. 2 is the subgroup analysis for MACEs, showing almost no interaction except for age. Antiplatelet therapy showed no beneficial trend in patients $\geq$ 65 years old. All-cause deaths were numerically lower in patients with antiplatelet therapy than in those without it.

5. Discussion

The present study showed the impact of anti-platelet therapy on MACEs for patients with VSA in a multicenter registry in Japan. Anti-platelet therapy had no marked impact on MACEs. To our knowledge, this is the first Japanese multicenter registry to investigate the effects of anti-platelet therapy on patients with VSA.

Previous clinical studies showed controversial results concerning the usage of anti-platelet therapy in VSA patients. Ishi et al. reported that low-dose aspirin did not affect cardiovascular events in VSA patients with non-significant stenosis in their single-center study during a mean follow-up period of 49 months (P = 0.541) [9].

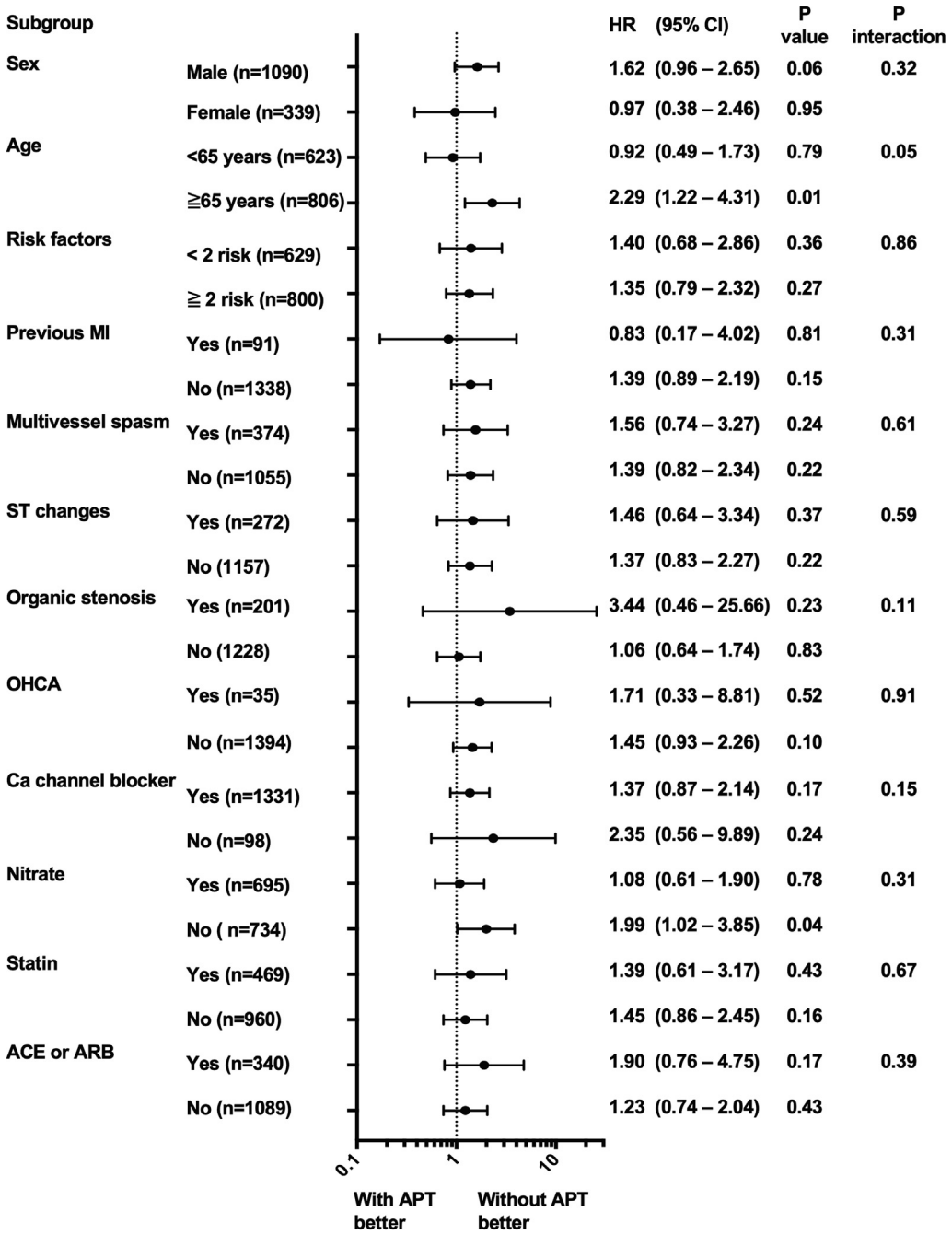

Fig. 2. A subgroup analysis of MACEs. MI = myocardial infarction, OHCA = out of hospital arrest, ACE = angiotensin-converting enzyme inhibitor, ARB = angiotensin-II receptor blocker.

However, in another single-center study of VSA with non-significant stenosis, during a median follow-up period of 52 months, VSA patients taking low-dose aspirin had a significantly higher incidence of MACEs than those without low-dose aspirin in a propensity score matching analysis (hazard ratio [HR] 1.54; 95% confidence interval [CI], 1.04–2.28; p = 0.037) [10]. Therefore, the significance of anti-platelet therapy remains unclear.

Importantly, a substantial number of case reports (mainly from Asia) have described thrombus formation following persistent coronary spasm [11–16]. These patients likely have frequent and persistent symptom that may be accompanied by spontaneous ST-elevation. Therefore, we cannot easily deny the usefulness of anti-platelet therapy in such severe VSA patients. In other basic studies, coronary spasm itself has been shown to increase the thrombogenicity, such as the fibrinopeptide A or soluble P-selectin levels, during the acetylcholine provocation test [17–19]. Furthermore, a previous intravascular imaging study using optical coherence tomography showed that substantial proportions of spasm sites had luminal irregularity [20–21], which pathologically suggests surface thrombus [22]. Thus, there may be a close relationship between thrombus formation and persistent spasm.

A recent study by Lee et al. investigated the impact of aspirin in 162 patients with vasospasm-related ACS [23]. In this population, aspirin significantly reduced the risk of myocardial infarction (HR 0.13; 95% CI 0.03–0.61; P = 0.014) and chest pain recurrence (HR 0.29; 95% CI 0.12–0.71; P = 0.006). The incidence rate of myocardial infarction during follow-up was 7.4% (15 of 162 patients). In

contrast, the incidence rate of myocardial infarction during follow-up in our study was only 0.6% (9 of 1429) and was<2% in previous studies by Lim and Ishii et al. [1024]. Therefore, the study populations in previous studies as well as our own seem to have included subjects with a non-severe condition and may be resemble the populations in studies for primary prevention of low-dose aspirin. The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial was a randomized, open-label trial examining the effect of low-dose aspirin in 2539 Japanese patients with type 2 diabetes without preexisting cardiovascular disease. It showed that low-dose aspirin did not reduce cardiovascular events (HR 1.14; 95% CI 0.91–1.42; P = 0.2) but did increase risk of gastrointestinal bleeding at the 10-year follow-up [25]. However, even in a sub-group analysis, our study failed to find any clear benefit of anti-platelet therapy, presumably due to the population having a low event rate.

The baseline characteristics before matching were significantly worse in patients with APT than in those without APT for most of the risk factors in our study, including the sex, age, coronary risk factors, history of MI, ST-changes and organics stenosis in our study. However, in the entire cohort, no marked differences in MACE were noted. Of note, this trend was similarly observed in the study by Ishi et al. [24]. How these baseline characteristics affect MACE in patients with VSA remains unclear. In a previous study from our group, history of out-of-hospital cardiac arrest, smoking, angina at rest alone, organic coronary stenosis, multivessel spasm, ST-segment elevation during angina and beta-blocker use were found to be predictors of MACE [26]. A comprehensive assessment as well as further studies are needed to understand the prognostic factors.

5.1. Limitations

The present study could not avoid the limitations inherent to multicenter observational studies performed in both retrospective and prospective manners. The management decisions were left to the discretion of each attending physicians, and the prescription of anti-platelet therapy was not randomized. Information on the details of medical treatment, such as low-dose aspirin, P2Y12 inhibitor and number of anti-platelet drugs, was not sufficient. Although a propensity score-matched analysis was performed, our analysis may still have failed to correct for unmeasured variables that could have affected the results. The low event rate and relatively short period for observational period were other factors that made the results of this study difficult to interpret. Also missing from this study was information on bleeding events, which is essential for understanding the benefits of antiplatelet therapy [27], as the efficacy of antiplatelet therapy can be hampered by bleeding events. However, this was the first multicenter registry study to investigate the impact of antiplatelet therapy, so we still believe that our study has merit.

6. Conclusion

Antiplatelet therapy exerted no beneficial effects on MACEs for VSA patients in a Japanese multicenter registry study. Further studies will be necessary to clarify which VSA patients can benefit from antiplatelet therapy.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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