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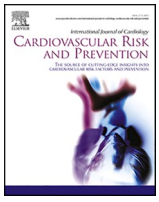

Real-world antithrombotic strategies in patients with atrial fibrillation and recently developed acute coronary syndrome

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ABSTRACT

Background: The antithrombotic strategy for patients with atrial fibrillation (AF) and coronary artery disease following percutaneous coronary intervention is shifting towards less intensive. Nevertheless, for patients with AF and acute coronary syndrome (ACS), an optimal antithrombotic strategy is yet to be established.
Methods and results: We conducted a multi-center cohort study involving 146 Japanese centers that had prospectively registered 460 patients with AF and ACS followed for 2 years. Primary endpoint was the composite of thrombotic and bleeding events, and secondary endpoints included heart failure hospitalization. At the time of study registration, 86 % of participants had received direct oral anticoagulants (DOACs) and 75 % had received aspirin-based triple antithrombotic therapy (TAT) between March 2017 and August 2019. Apixaban was the most frequently used DOAC (29 %). While the proportion of anticoagulants did not change according to the time course, the intensity of antiplatelets significantly attenuated over time (dual antiplatelet at baseline: 75 %, and at 2-years: 7 %). The cumulative incidence of the primary outcome measure was similar in patients with warfarin and DOACs. However, the risk of heart failure hospitalization was significantly higher in those with warfarin compared to DOACs (Hazard ratio: 2.8, 95 % confidence interval: 1.1–5.8, p = 0.022).
Conclusions: The present findings suggest the appropriate optimization of antithrombotic medication balancing in patients with AF and ACS in Japan by reducing the intensity of antiplatelets during the study period.

1. Introduction

For patients with coronary artery disease (CAD) and who have undergone percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) using aspirin and P2Y12 inhibitors at least for a year has long been the gold standard antithrombotic regimen [1,2], and oral anticoagulation is the established antithrombotic treatment for patients with atrial fibrillation (AF) [3,4]. Therefore, for patients with AF following PCI, accounting for 5–10 % of all PCI patients [5], triple antithrombotic treatment (TAT), DAPT plus an anticoagulant, has been indicated. However, the recent trend in the antithrombotic strategy has been shifting to medications represented by the notion “less is more” in terms of not only reducing the number of regimens, but also shortening the duration of antithrombotic medications in this population [6], since TAT has been identified as the major risk factor of critical bleeding [7]. Moreover, a landmark trial involving patients with a history of stable CAD and AF demonstrated the significant benefit of oral anticoagulation monotherapy more than a year after the PCI procedure to reduce the risk of bleeding, while maintaining antithrombotic efficacy with double antithrombotic therapy (DAT) [8]. However, in patients with acute coronary syndrome (ACS) and AF following emergent or urgent unplanned PCI, evidence for determining the optimal regimens and durations of antithrombotic strategy is still insufficient. Although recent guidelines recommend the shorter duration of TAT in AF patients after PCI [9], there might be a certain population who may need to continue that beyond 1 month, when patients have a very high risk for stent thrombosis which outweighs bleeding risk [7]. Therefore, the antithrombotic strategy for maximizing the safety and efficacy should be determined by risk stratification based on the net benefit by balancing the thrombotic/ischemic and bleeding risk in individual patients.

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Nevertheless, evidence for determining the optimal antithrombotic strategy among various alternatives is still insufficient in patients with ACS and AF.

To clarify the actual situations surrounding an antithrombotic strategy in patients with ACS and AF, including regimens, combinations, durations, mid-term efficacy, and safety outcomes, the present multicenter observational study prospectively registered individuals who had undergone PCI for ACS and were administered any anticoagulant for AF at the time of discharge from hospitalization due to ACS treatment. Moreover, this study followed the temporal changes in prescriptions and their efficacy and safety outcomes for 2 years. (Study of Real World Anticoagulation and Antiplatelet Practice in Patients with Acute Coronary Syndrome Complicated with Atrial fibrillation: STAR-ACS study).

2. Patients and methods

The STAR-ACS study was designated to explore the real-world clinical circumstances in patients with ACS and AF with respect to antithrombotic strategies, such as the regimens, doses, and durations, and the incidences of thrombotic and bleeding events at the time of the study. In particular, this study focused on the assessment of the net risk/benefit according to the type of anticoagulant (warfarin vs. DOACs) and the number of antiplatelets (oral anticoagulant only, single and dual antiplatelets, SAPT and DAPT). All data were collected via an electrical data capture (EDC) system (DDworks21/EDC plus (Suite), Fujitsu Ltd., Tokyo, Japan). This study is publicly registered via University Medical Information Network Japan-Clinical Trials Registry (UMIN-CTR) (ID: UMIN000027356).

2.1. Study eligibility

This study is a retrospective observational analysis of a prospective multi-center ~~observational~~ cohort ~~study~~ of registered patients with diagnosis of ACS and AF which enrolled 147 centers in Japan. Attending cardiologists at each participating center diagnosed ACS, including ST-elevation myocardial infarction (STEMI), non ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), in accordance with the universal definition of myocardial infarction [10], in patients who required an unplanned emergent or urgent PCI procedure, and with paroxysmal, persistent, or permanent AF requiring any of the oral anticoagulants (warfarin or 4 types of DOACs) [3,11]. After obtaining written informed consent, eligible patients were prospectively enrolled in the study at the time of their discharge from hospital for the treatment of ACS between April 1, 2016 and August 7, 2019. Patients with ACS which was caused by any coronary revascularization procedure, including PCI or coronary artery bypass graft surgery were not eligible for inclusion. Details of the inclusion and exclusion criterions for the study are presented in Supplementary Table 1.

2.2. Follow-up

At the time of study registration, data on background demographic characteristics, including types of ACS and AF and risk scores of thrombosis and bleeding (CHA_2DS_2-VASc and HAS-BLED scores), comorbidities, echocardiographic data (left ventricular ejection fraction: LVEF), laboratory findings, and medications were collected. Study participants were followed-up for 2 years from study registration. Data on physical condition, blood tests, and medications were collected at the time of occurrence of primary and secondary outcome measures and at one year and at two years following registration with three months allowance.

2.3. Outcome measures and group comparisons

The primary outcome measure in the present study was the composite of major bleeding in accordance with the definition of the International Society of Thrombosis and Hemostasis (ISTH) [12] and major adverse cardiovascular events (MACE) consisting of cerebral and cardiovascular death, non-fatal ACS, non-fatal stroke, and stent thrombosis. Secondary endpoints included bleeding death, non-cardiovascular death, acute heart failure requiring hospitalization, transient ischemic attack (TIA) requiring hospitalization, coronary revascularization, target vessel failure, endovascular treatment for peripheral arteries including a carotid artery, aortic disease (aneurysm and dissection), and embolism and cancer (new-onset and relapse) in addition to each component of the primary endpoint. The occurrence of outcome measures was compared in predefined subgroups with types of anticoagulants (warfarin vs. DOACs), number of antiplatelets (0,1 vs. 2), and high vs. low bleeding/thrombotic risk stratified by HAS-BLED ($<$vs. $\geq$3) and CHA2DS2-VASc ($<$vs. $\geq$2) scores [13,14].

2.4. Sample size determination

A previous registry-based observational study enrolling 3597 Japanese ACS patients demonstrated that the prevalence of AF among Japanese ACS patients was 4.3 % [16]. The number of participating centers in the present study was estimated to be between 100 and 150, which accordingly suggested that the total number of ACS patients in the present study was approximately 10,000 [15]. Therefore, we have estimated the number of patients with ACS and AF in the present study to be about 400–450.

2.5. Statistical analysis

Continuous variables are presented as the mean $\pm$ standard deviation or median with interquartile range (IQR) in accordance with the results of the Shapiro-Wilk normality test. Categorical variables are presented as the actual number and frequencies (%). Quantitative data across groups were compared using the ANOVA test or the Kruskal-Wallis test as appropriate. Categorical variables were compared using the Fisher-exact test with the chi-squared test. The Cochran-Armitage test was used to evaluate the temporal changes of medications (at baseline, 1-year, and 2-year follow-up). Parametric Pearson correlation analysis was used to evaluate the correlation between the risk scores of thrombotic events and bleeding. In the survival analysis, the cumulative 2-year incidences of primary and secondary outcome measures and 95 % confidence intervals (CI) were calculated for the entire subject population and predefined subgroups using the Kaplan-Meier method followed by log-rank comparisons. The hazard ratios (HR) with 95 % confidence intervals (95 % CI) of a patient group relative to the reference group for the primary and secondary outcome measures were obtained by Cox proportional-hazard analyses using the age- and sex-adjusted model. All reported P values are 2-sided and were considered as significant when $<$0.05. Data were analyzed with SAS 9.2 (SAS Institute Corp, Cary, NC) and R4.2.

2.6. Ethics

This study was conducted in accordance with the Declaration of Helsinki. Ethics approval was granted by the Juntendo University Clinical Research Committee (research reference number: 16–010), and by ethics committees at all participating sites. All participants provided written informed consent.

3. Results

3.1. Background demographics and antithrombotic medications in entire study population

During the more than 3-year period of registration (April 2016 to August 2019), 460 patients were prospectively registered to participate in the present study. After excluding 10 individuals due to withdrawal of

participation and/or study protocol violation, including incorrect registration of patients who only underwent thrombectomy as the PCI procedure (n = 8), 450 patients were finally included in the analysis. The follow-up completion rate for 2 years in the present study was 100 % (first patient in: March 31, 2017, and last patient out: Oct 26, 2021) (Supplementary Fig. 1: A flow diagram of the study). Based on previous observational studies regarding the complication rate of AF in ACS patients ranging from 4 % to 11 % [16–18] and a questionnaire survey for participating institutions regarding the number of ACS during study registration, the background number of ACS patients in this study could be estimated to be more than 10,000. The prevalence of STEMI was highest (57.7 %) among the types of ACS and that of paroxysmal type was highest among the types of AF (51.3 %). In combination with ACS and AF types, the ratio of patients with STEMI and paroxysmal AF was

Table 1
Background demographics of total participants, warfarin group and DOAC group.

		Total Participants (n = 450)	Warfarin group (n = 65)	DOAC group (n = 385)	p-value (Warfarin vs. DOAC groups)
Age		75 ± 9.0	75.1 ± 9.2	74.8 ± 1.0	0.8
	≥65 years old	395 , 88 %	57 , 88 %	338 , 88 %	1.0
	≥75 years old	258 , 57 %	37 , 57 %	221 , 57 %	1.0
Sex, female		91 , 20 %	10 , 15 %	81 , 21 %	0.4
History of stroke		84 , 19 %	14 , 22 %	70 , 18 %	0.6
	Ischemic*	78 , 17 %	13 , 20 %	65 , 17 %	0.6
	Non-ischemic	8 , 2 %	2 , 3 %	6 , 2 %	0.6
History of	Myocardial infarction	64 , 14 %	15 , 23 %	49 , 13 %	0.0
	Heart failure	43 , 10 %	12 , 18 %	31 , 8 %	0.0
	Bleeding events*	22 , 4 %	5 , 8 %	13 , 3 %	0.2
	Valvular disease*	22 , 5 %	6 , 9 %	16 , 4 %	0.1
	Malignancy*	64 , 14 %	8 , 12 %	55 , 14 %	0.8
Hypertension		413 , 92 %	60 , 92 %	353 , 92 %	1.0
Diabetes		176 , 32 %	39 , 60 %	137 , 36 %	**<0.0001**
Chronic kidney disease		98 , 0.218	31 , 48 %	67 , 17 %	**<0.0001**
	Serum creatinine	2.14 ± 2.34	1.2 ± 1.3	1.1 ± 0.5	0.7
	eGFR	35.71 ± 14.2	56.9 ± 18.6	52.1 ± 17.3	0.1
Smoking	Current	116 , 26 %	21 , 32 %	95 , 25 %	0.4
	Past	176 , 39 %	23 , 35 %	153 , 40 %	
Ejection Fraction (%)		51.4 ± 11.4	51.8 , 11.3	49.1 , 11.6	0.1
AF types	Paroxysmal	231 , 51 %	24 , 37 %	207 , 54 %	**0.004**
	Persistent	94 , 21 %	12 , 18 %	82 , 21 %	
	Permanent	125 , 28 %	29 , 45 %	96 , 25 %	
ACS types	STEMI	259 , 58 %	32 , 49 %	227 , 59 %	0.3
	NSTEMI	103 , 23 %	16 , 25 %	87 , 23 %	
	Unstable angina	88 , 20 %	17 , 26 %	71 , 18 %	
Culprit lesion of ACS	LAD	224 , 50 %	35 , 54 %	189 , 49 %	0.6
	LCx	105 , 23 %	17 , 26 %	88 , 23 %	0.7
	RCA	172 , 38 %	24 , 37 %	148 , 38 %	0.9
	LM	18 , 4 %	2 , 3 %	16 , 4 %	1.0
	Others	0 , 0 %	0 , 0 %	0 , 0 %	1.0
CHA2Ds2-VASc score	Mean	4.6 ± 1.6	4.9 ± 1.8	4.5 ± 1.5	0.1
	0	1 , 0 %	0 , 0 %	1 , 0 %	0.4
	1	5 , 1 %	0 , 0 %	5 , 1 %	
	2	30 , 7 %	5 , 8 %	25 , 6 %	
	3	63 , 14 %	8 , 12 %	55 , 14 %	
	4	133 , 30 %	19 , 29 %	114 , 30 %	
	5	109 , 24 %	13 , 20 %	96 , 25 %	
	6	50 , 11 %	7 , 11 %	43 , 11 %	
	7	40 , 9 %	6 , 9 %	34 , 9 %	
	8	17 , 38 %	6 , 9 %	11 , 3 %	
	9	2 , 0 %	1 , 2 %	1 , 0 %	
HAS-BLED score	Mean	3.1 ± 0.9	3.5 ± 1.1	3.1 ± 0.8	**0.001**
	0	1 , 0 %	0 , 0 %	1 , 0 %	**0.0005**
	1	9 , 2 %	2 , 3 %	7 , 2 %	
	2	67 , 15 %	8 , 12 %	59 , 15 %	
	3	253 , 56 %	24 , 37 %	229 , 59 %	
	4	96 , 21 %	19 , 29 %	77 , 20 %	
	5	18 , 4 %	9 , 14 %	9 , 2 %	
	6	6 , 1 %	3 , 5 %	3 , 1 %	
Anticoagulants	Warfarin	65 , 14 %	65 , 100 %	0 , 0 %	N/A
	Apixaban	132 , 29 %	0 , 0 %	132 , 34 %	N/A
	Rivaroxaban	77 , 17 %	0 , 0 %	87 , 23 %	
	Edoxiaban	115 , 26 %	0 , 0 %	115 , 30 %	
	Dabigatran	31 , 11 %	0 , 0 %	51 , 13 %	
Sort of Antiplatelets	Any antiplatelet	442 , 98 %	63 , 97 %	379 , 98 %	0.6
	Aspirin	354 , 79 %	55 , 85 %	299 , 78 %	0.3
	Clopidogrel	240 , 53 %	31 , 48 %	209 , 54 %	
	Prasugrel	186 , 41 %	28 , 43 %	158 , 41 %	
	Cilostazol	1 , 0 %	0 , 0 %	1 , 0 %	
	Ticagrelor	1 , 0 %	0 , 0 %	1 , 0 %	
Combination of antiplatelets	SAPT	103 , 23 %	12 , 18 %	91 , 24 %	0.4
	DAPT	338 , 75 %	51 , 78 %	287 , 75 %	0.6
	No antiplatelet	8 , 0 %	2 , 3 %	6 , 2 %	0.3

highest (31.1 %) followed by those with STEMI and permanent AF (15.1 %) (Supplementary Fig. 2). The average age of the study patients was 75 years and the proportion of individuals older than 75 years was 57.3 %. The ratios of patients with a history of stroke, myocardial infarction, heart failure, and any major bleeding event were 18.7 %, 14.2 %, 9.6 %, and 4.0 %, respectively. The majority of participants were at high risk for both thrombotic and bleeding events, (47.1 % of study participants had CHA_2Ds_2-VASc score ≥4 and HAS-BLED score ≥3) (Table 1, Total participants). Moreover, both bleeding and thrombotic risk scores were strongly correlated with each other (Fig. 1). For anticoagulants, warfarin was administered to 14.4 % of patients, while others (85.6 %) received DOACs. Among DOACs, apixaban was the most often administered (29.3 %) followed by edoxaban (25.6 %), rivaroxaban (19.3 %), and dabigatran (11.3 %) (Fig. 2a). Aspirin was the most prescribed antiplatelet (78.7 %) followed by clopidogrel (53.3 %) and prasugrel (41.3 %) at baseline. Three quarters of the patients received two types of antiplatelets (DAPT: 75.1 %) in addition to an anticoagulant (TAT) at baseline and the ratio without any antiplatelet was very limited at baseline (1.8 %) (Fig. 2b).

3.2. Temporal changes of antithrombotic and other medications

While all of the enrolled patients could be prescribed any of the anticoagulants for study participation, antiplatelets were not mandatory. At baseline, and 1- and 2-year follow-up, there was no significant change in the type of anticoagulants, not only in the proportion of receiving warfarin compared to DOACs, but also the distributions of DOACs (Fig. 3a). In contrast, the proportions of patients taking an antiplatelet medication drastically and significantly decreased over time for all 3 drugs (Fig. 3b). Notably, more than 90 % of participants took no (only OAC) or a single antiplatelet (SAPT) at 2-year follow-up, although 75 % of patients were prescribed dual antiplatelets (DAPT), in other words aspirin plus one P2Y12 inhibitor, at the time of study registration (Fig. 3c). For lipid lowering treatment, while the ratio of taking statins was similar throughout the study period, that of ezetimibe had significantly increased. The beta blocker and angiotensin converting enzyme/angiotensin receptor blocker (ACEI/ARB) usage ratios did not change during the follow-up period (Supplementary Fig. 2).

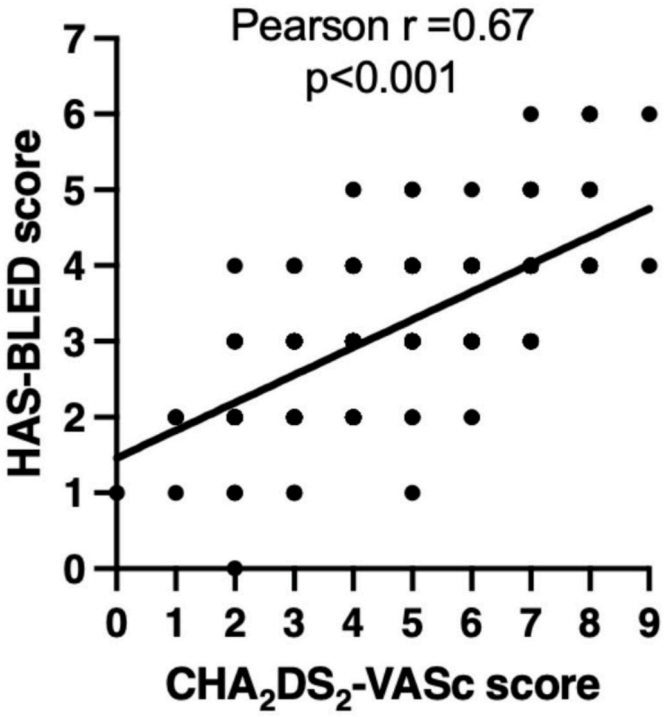

Fig. 1. Correlation between HAS-BLED score and CHA_2DS_2-VASc score.
r: Pearson's correlation coefficient.

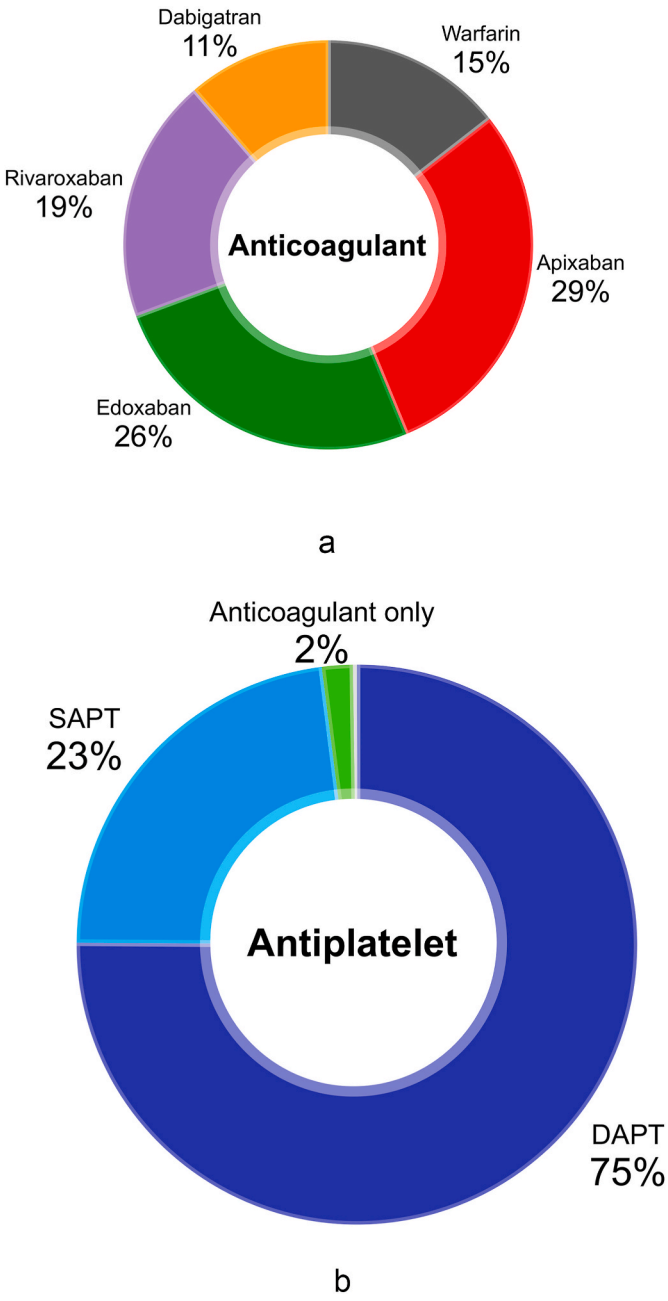

Fig. 2. Distributions of anticoagulants (a), and number of antiplatelets (b) at study registration.
DAPT: dual antiplatelet therapy (DAPT), single antiplatelet therapy (SAPT).

3.3. Comparisons of baseline characteristics between patients who received warfarin or DOACs as oral anticoagulant for AF

Among the patients who received warfarin at baseline (Warfarin group), at the discharge from the hospital for ACS treatment, the proportions of patients with a history of heart failure and myocardial infarction, and complication of diabetes and chronic kidney disease (CKD) were significantly higher compared to those who were administered DOACs (DOAC group). Moreover, the ratio of permanent AF was significantly higher in the Warfarin group than the DOAC group, although there was no difference in the types of ACS. Both the thrombotic and bleeding risk scores were numerically higher in the Warfarin

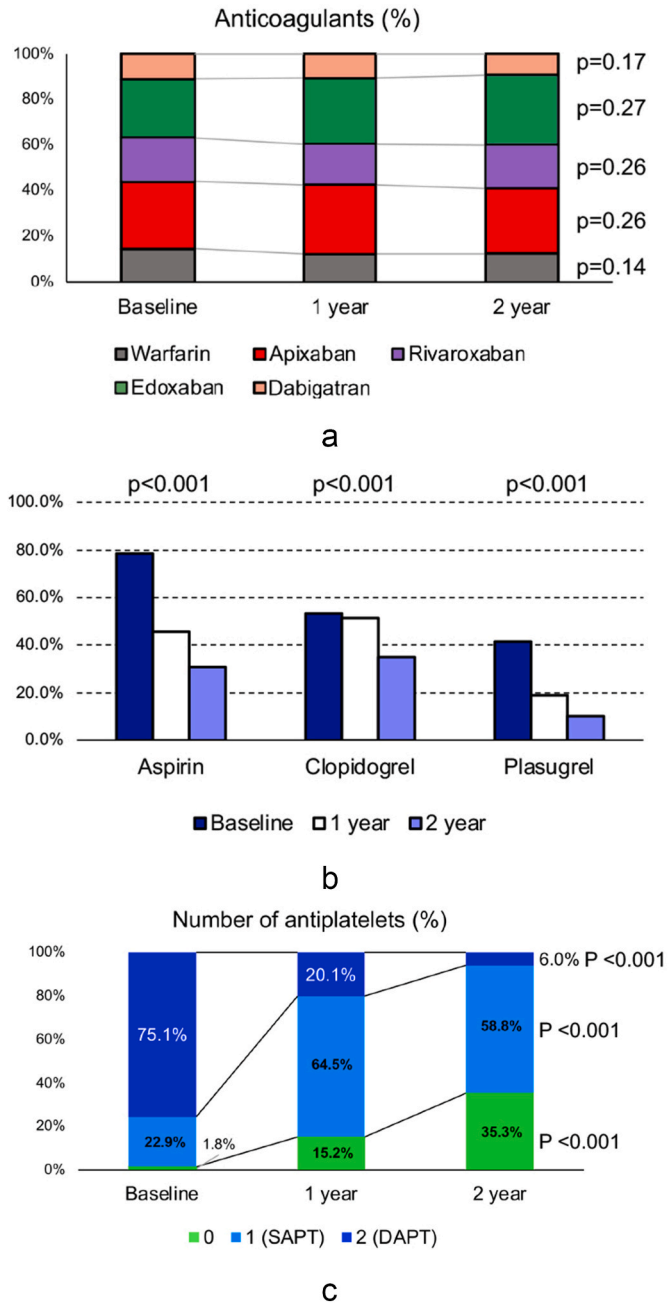

Fig. 3. Temporal changes of antithrombotic medications.
a: anticoagulants, b: antiplatelets and c: number of antiplatelets through baseline (study registration), 1-year and 2-year follow-up. Trends were assessed by the Cochran-Armitage test. SAPT: single antiplatelet therapy, DAPT: dual antiplatelet therapy.

group compared to DOAC group, although its difference did not reach statistical significance. Consistently, the proportion of patients with high bleeding risk (HAS-BLED score of 4 or more) was significantly greater in the Warfarin group (48 %) than the DOAC group (23 %). The number and type of antiplatelets were similar between the groups (Table 1, Warfarin vs. DOAC groups).

3.4. Cumulative incidences of primary and secondary outcome measures in entire study population, and patients with warfarin vs. with DOACs within 2 years of study registration

The overall cumulative incidences of the primary outcome measure, the composite of cerebrocardiovascular events, and ISTH major bleeding in the entire study population, were 10.0 % (57.5/1000 person-years), 7.4 % (41.9/1000 person-years), and 3.9 % (22.1/1000 person-years), respectively. The incidences of other predefined endpoints are listed in Supplementary Table 1. Although the log-rank comparison did not reach statistical significance, the cumulative incidence of the primary outcome measure tended to be higher in patients with warfarin compared to those with DOACs, while those of ISTH major bleeding were very similar in the two groups (Fig. 4a and **b**). In contrast, heart failure hospitalization was significantly more frequent in patients with warfarin compared to DOACs (Fig. 4c). Adjusted Cox proportional hazard analyses using two models showed that DOACs were independently associated with a decreased risk of heart failure hospitalization, while that was not the case for primary outcome measure, ISTH major bleeding, or the composite of cerebral cardiovascular events (Supplementary Table 2). Interestingly, the proportion of patients receiving DAPT in addition to an anticoagulant, those with TAT, was significantly higher in patients receiving warfarin, compared to those with DOACs at 2-year follow-up (16.9 % vs. 4.1 % $p = 0.002$), even though there was no significant difference at baseline or 1-year follow-up (Supplementary Fig. 4).

4. Discussion

The STAR-ACS study investigated the real-world situations of antithrombotic strategies, actual incidences of bleeding and thrombotic events, and overall outcomes in patients with both AF and ACS who underwent PCI in Japan between 2016 and 2019. As anticoagulants for AF in patients who had recently developed ACS and undergone unplanned PCI, DOACs were used for the majority of patients compared to warfarin, while the ratios of DOACs and warfarin had not changed for 2 years since the end of hospitalization for ACS treatment. Among four DOACs, apixaban and edoxaban were more frequently used than rivaroxaban and dabigatran, and the order of DOACs did not change during follow-up. In contrast, for antiplatelet drugs administered together with anticoagulant drugs, the prescription rates of aspirin, clopidogrel and prasugrel had significantly decreased during the clinical course. Similarly, the number of antiplatelets decreased significantly during 2-year follow-up. The overall annual incidence of the primary outcome measure, which was the composite of ISTH major bleeding, cerebral and cardiovascular death, non-fatal ACS, non-fatal stroke, and stent thrombosis, was 5.1 %. The incidences of cardiovascular death and ISTH major bleeding for 2 years were 3.3 % and 3.9 %, respectively. In the prespecified group comparison, in patients who received warfarin for AF, the prevalence of a history of myocardial infarction and heart failure, diabetes, chronic kidney disease, and advanced type of AF with high bleeding risk (higher HAS-BLED score) were significantly higher than in those who received DOACs. The cumulative incidence of the primary outcome measure in patients with warfarin at baseline was slightly higher, although the difference did not reach statistical significance, while the incidence of ISTH major bleeding was almost identical in the two groups. In contrast, log-rank comparison showed a significantly higher cumulative incidence of heart failure hospitalization in patients with warfarin compared to those with DOACs.

Previous studies have explored the relationship between AF and ACS through multiple perspectives. As CAD and AF share similar risk factors and pathophysiological mechanisms, they are the most common forms of atherosclerotic cardiovascular disease and sustained cardiac arrhythmias [16]. Previous studies have demonstrated that approximately 10–20 % of patients with AF have concomitant CAD [17] and 6–7% of CAD patients who undergo PCI have AF [5]. Moreover, the complication rate of AF in patients with ACS is higher than in those with chronic coronary syndrome (CCS) [18,19]. Meanwhile, an observational study reported an increased risk of the development of AMI in individuals who were recently diagnosed with AF [20]. Despite such a close clinical relationship between AF and ACS, the prevalence of subtypes and possible correlation of the disease severity or duration of AF and ACS has

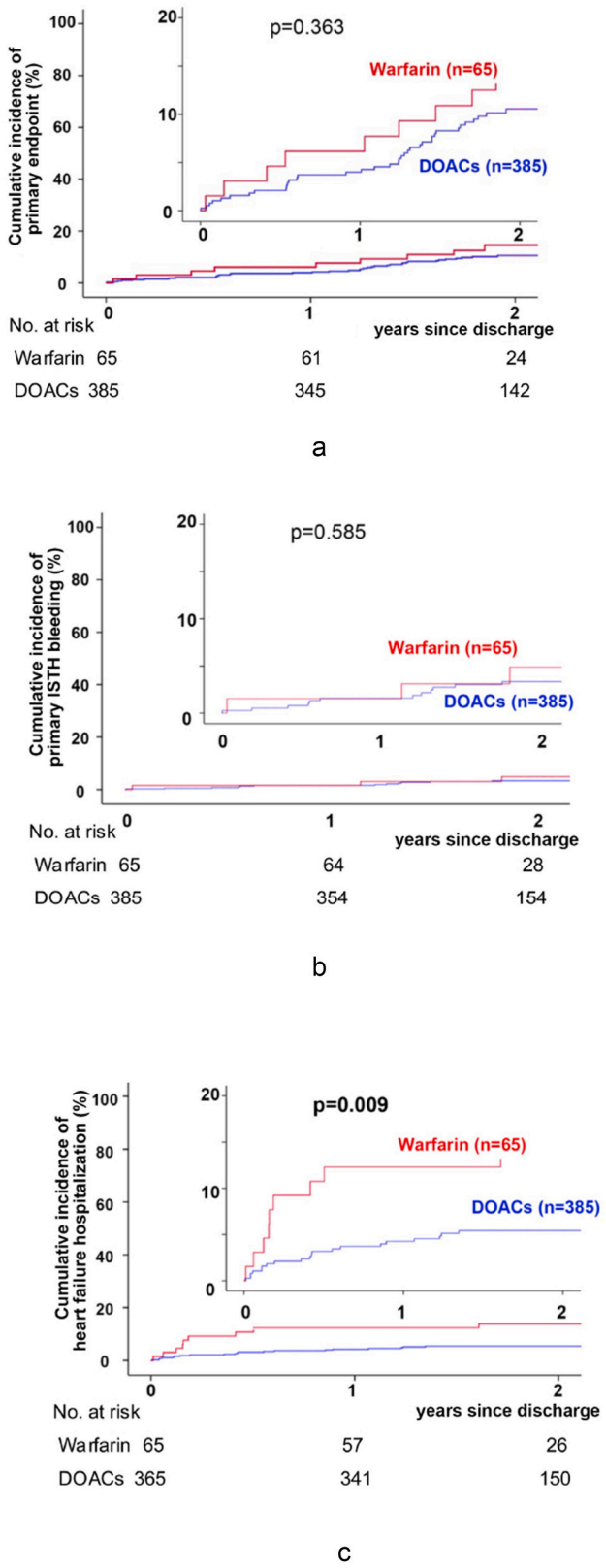

Fig. 4. Cumulative incidences of primary outcome measure, ISTH major bleeding and heart failure hospitalization.

Cumulative incidences of primary outcome measure (a), International society of thrombosis and haemostasis (ISTH) major bleeding (b) and heart failure hospitalization (c). p: p-values in log-rank comparisons, DOACs: direct oral anticoagulants.

not been fully evaluated. In the present study, the incidence of patients who had both STEMI and paroxysmal AF was the greatest (>30 %), while those of patients who had UA and paroxysmal AF (mildest form of ACS and shortest duration of AF) or both STEMI and permanent AF (severest type of ACS and longest duration of AF) were less than 10 %, indicating the severities of ACS and/or disease duration of AF were not directly correlated in this study population. As new-onset AF is one of the major complications of STEMI [21], STEMI patients who developed new-onset AF might have included those with STEMI and paroxysmal AF in this study. In light of the outcomes following ACS, the complication of AF was associated with significantly increased risk of poor outcomes. An observational cohort study and a meta-analysis found that the presence of AF in patients with ACS or AMI was associated with a significantly higher risk for all-cause mortality [22]. Moreover, the risk of subsequent hospitalization due to heart failure is also increased by AF in AMI patients [23]. In this study, the incidence of net cardio-cerebellar and bleeding events, all-cause death, and ISTH major bleeding were relatively lower than those in previous studies [24], mainly because in-hospital CV events were excluded, as participants were registered in the study at the end of hospitalization for ACS treatment.

The efficacy vs. safety, and benefit vs. risk regarding antithrombotic medications in patients with AF and CAD have been extensively evaluated, as anticoagulants for reducing the risk of thromboembolism in AF patients cannot be replaced by antiplatelets. However, in patients with AF and ACS, the optimal antithrombotic regimen and its duration in accordance with the time course following ACS still remains to be established and a matter of intense debate. Even though warfarin has been the gold standard anticoagulant for a long time, it has several significant limitations, including a narrow therapeutic window, drug interactions, and the need for frequent monitoring of its efficacy. In contrast, DOACs have emerged as a promising alternative to warfarin for patients with AF for more than 10 year [25]. Based on major trials and their metanalyses constantly demonstrating that DOACs were non-inferior in terms of efficacy and superior in the safety, guidelines have recommended DOACs rather than warfarin [3,11,26]. Previous randomized trials of DOACs in patients with AF who underwent PCI and their meta-analyses have consistently demonstrated the net-benefit of DOACs, compared to warfarin, when they were combined with any antiplatelet to reduce bleeding risk while maintaining antithromboembolic efficacy [24,27]. Particularly, in a subanalysis of the AUGUSTUS study, it was found that apixaban had a greater net benefit than warfarin in patients with AF and recent ACS [38] who had undergone elective PCI [28]. In the present study, apixaban and edoxaban were more frequently used among DOACs. Previous studies has suggested the superiority of safety in these two DOACs [29,30], while All DOACs were found to be similarly effective in preventing mortality, strokes and systemic embolisms [31] (PMID: 31329212). Accumulating evidence may have influenced the prescribing trends observed in this study.

Among various combinations of antithrombotic medications, previous studies have reported an increased risk of major bleeding or clinically relevant non-major bleeding by aspirin-based triple antithrombotic therapy (TAT) in patients with AF and ACS, while it has been shown to reduce the risk of thrombotic events [32]. The WOEST trial compared TAT consisting of aspirin, clopidogrel and warfarin, to double therapy consisting of TAT without aspirin in patients undergoing PCI, and observed that TAT was associated with a higher risk of major bleeding [7]. These previous findings suggest that the comprehensive risk in a patient with AF and ACS requiring PCI should be individually and multifacetedly estimated by background demographics, comorbidities, clinical setting, and the complexity of coronary lesions in each patient for maximizing the net benefit. In the present study, none of the comparisons of antithrombotic regimens, such as DOACs vs. warfarin, aspirin vs. P2Y12 inhibitors, and TAT (aspirin-based DAPT plus anticoagulant) vs. DAT (aspirin- or P2Y12 inhibitor-based SAPT plus anticoagulant), found any significant differences in the incidences of cardiovascular and bleeding events. These findings might suggest the

precise fine tuning of antithrombotic regimens and their durations by the Japanese attending cardiologists at participating institutions, who ~~deeply~~ understood and appreciated the risk/benefit of antithrombotic medications in this particular population, and properly reduced the numbers and doses of antithrombotic agents in individual patients at the appropriate time points. During the present study period, a series of STOP-DAPT studies revealed the net benefit of shorter duration of DAPT with a significantly lower rate of a composite of cardiovascular and bleeding events in patients with CAD, including approximately 40 % of ACS patients who underwent PCI [19,33]. Accordingly, the present results reflect the trends in antithrombotic medication administration, which have drastically changed in accordance with the notion "less is more" during the period of this study.

The present study showed a significant relationship between warfarin use and the increased risk of heart failure hospitalization. While the incidences of pre-existing and new-onset AF were similar in patients receiving warfarin and DOACs, the duration of AF was significantly longer in those on warfarin. Additionally, the prevalence of valvular disease was not significantly but was numerically higher in patients with warfarin. Since the use of DOACs has been prohibited in Japan in patients with severely impaired kidney function, renal function was further impaired in patients with warfarin in this study. Although the Cox proportional hazard analysis was adjusted for renal function and a history of heart failure, a significantly longer history of AF in patients with warfarin might have a pathological impact on the subsequent higher incidence of heart failure hospitalization. From the ACS perspective, there were no significant differences in the distribution of coronary culprit lesions or types of procedures between patients with warfarin and DOACs. Accordingly, the higher incidence in heart failure might have been caused by factors related to AF rather than ACS/CAD.

5. Limitations

This study has several limitations. First, because of the relatively small sample size and various combinations or doses and durations of antithrombotic medications, evaluating the contribution of each of these to the risk of cardiovascular, thromboembolic, and bleeding events might be underpowered, which may obscure any potential significance in this study. Therefore, further investigations with larger sample sizes are needed to assess the associations between each of the thrombotic regimens and outcomes in this population. Second, the retrospective nature of the analyses other than the prespecified primary outcome measure may not be suitable to infer causality. Moreover, even though the effects of warfarin at baseline for heart failure hospitalization, which was one of the secondary outcome measures, were adjusted by multivariate models, residual confounding factors which might explain the causation cannot be excluded. Third, while this study is a multicenter study with 147 centers participating, a setting involving only Japanese patients may limit the generalizability of the present findings. Fourth, this study is not a randomized trial and does not involve interventions, which presents limitations in comparing the effects of the medications.

6. Conclusions

Despite these limitations, this prospective observational study has certainly clarified the real-world circumstances regarding antithrombotic strategies in patients with AF, and recent ACS, including information on temporal changes in antithrombotic medication regimens in accordance with the ACS time course, as well as the 2-year outcome.

Disclosures

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Data availability

All data in this study will be available upon appropriate requests, which will be assessed by primary investigator.

CRediT authorship contribution statement

Hiroshi Iwata: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Katsumi Miyauchi:** Supervision, Conceptualization. **Shuko Nojiri:** Formal analysis. **Yuji Nishizaki:** Data curation. **Yuichi Chikata:** Writing – review & editing. **Hiroyuki Daida:** Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

Hiroshi Iwata: KOWA, MSD, Novo Nordisc, Bayer, Sumitomo Pharma, **Katsumi Miyauchi:** none, **Syuko Nojiri**: none **Yuji Nishizaki:** none, **Yuichi Chikata:** none, **Hiroyuki Daida**: Novartis, Bayer, Kowa, Taisho Pharma, Abbott Medical, Otsuka Pharma, Amgen, MSD, Daiichi Sankyo, Pfizer, Fukuda Denshi, Tsumura, Toa-Eiyo

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Appendix A. Supplementary data

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