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Cardiac Pharmacology

Comparative Effectiveness and Safety of Antithrombotic Therapy in Atrial Fibrillation Patients Presenting with Acute Coronary Syndrome or Percutaneous Coronary Intervention

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Background: There remains insufficient evidence to determine the optimal antithrombotic strategy in atrial fibrillation (AF) patients presenting with acute coronary syndrome (ACS) or percutaneous coronary interventions (PCIs), especially in Asian populations.

Objectives: This study aimed to examine the real-world patterns of antithrombotic treatment among these patients and to compare the effectiveness and safety of different antithrombotic regimens.

Methods: A retrospective cohort study was conducted in AF patients presenting with a new ACS or PCI during 2006/1/1-2016/4/1. Three antithrombotic regimens were compared: dual antiplatelet therapy (DAPT, as the reference group), triple therapy (TT: DAPT plus an oral anticoagulant), and dual therapy (DT: single antiplatelet plus an oral anticoagulant). The outcomes of interest were major adverse cardiac and cerebrovascular events (MACCEs) and bleeding. Treatment effect was estimated using a Cox proportional hazards model. Inverse probability of treatment weighting was used to balance baseline characteristics among comparison groups.

Results: Overall, 532 patients were included. At discharge from the index hospitalization, DAPT was the most common antithrombotic therapy, followed by TT and DT. No significant difference in MACCEs was found among the different antithrombotic regimens. However, DT was associated with a lower risk of any bleeding [adjusted hazard ratio 0.20 (95% confidence interval, 0.06-0.75)] than DAPT.

Conclusions: In the study population, DAPT was the most commonly prescribed antithrombotic regimen for cardio-cerebrovascular disease prevention. The effectiveness outcomes were comparable across different antithrombotic strategies. The lower risk of bleeding with DT compared with DAPT warrants further investigation.

Key Words: Acute coronary syndrome • Anticoagulants • Atrial fibrillation • Percutaneous coronary intervention • Platelet aggregation inhibitors

INTRODUCTION

It has been estimated that 5-8% of patients with underlying atrial fibrillation (AF) undergo percutaneous coronary interventions (PCIs),[1] and that 2.3-21% of all acute myocardial infarctions (AMIs) are complicated by AF.[2] Patients with coexisting conditions have been reported to have a higher risk of death,[1] so that the use of antithrombotic therapy is required to prevent cardiac and cerebrovascular events. Guideline-recommended

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antithrombotic regimens include dual antiplatelet therapy (DAPT) with aspirin and a P_2Y_{12} inhibitor; dual therapy (DT) with an antiplatelet agent and an oral anticoagulant; and triple therapy (TT) consisting of a combination of DAPT and an oral anticoagulant. However, the ideal antithrombotic strategy for these patients remains unknown, and the current guidelines have different recommendations.[3,4] The use of TT has raised concerns over the higher risk of bleeding and uncertain comparative effectiveness in preventing major adverse cardiac and cerebrovascular events (MACCEs) compared to DAPT and DT.[5-7] Furthermore, established epidemiologic data have revealed that Asian patients have a higher risk of overall stroke and intracranial hemorrhage than Caucasian patients.[8-10] Taken together, these findings suggest that there could be differences with regards to the antithrombotic regimens of choice in different races, and more studies are needed to guide the treatment in Asians. Therefore, the aim of this study was to compare the effectiveness and safety of different antithrombotic regimens in an Asian population using data from a medical center in Taiwan.

METHODS

This was a retrospective cohort study. The study protocol was approved by the Research Ethic Committee of the National Taiwan University Hospital (NTUH) (certificate number: 201611046RINA) and fulfilled the ethical guidelines of the 1975 Declaration of Helsinki. The need for informed consent from the patients was waived.

Data source

The Integrated Medical Database of National Taiwan University Hospital (NTUH-iMD) was used as our main data source. The database was created in 2006 and is composed of demographic data, diagnoses, operation notes, medical progress notes, laboratory tests, imaging studies, medication prescriptions, and death records. The electronic medical record (EMR) system was also used to retrieve data that were not included or completely recorded in the NTUH-iMD, such as social history, prior bleeding records, and PCI characteristics.

Participants

The subjects in this study were patients with underlying AF presenting with acute coronary syndrome (ACS) or a PCI. Patients aged ≥ 20 years with an AF diagnosis were enrolled. Among these patients, we further identified those who had a new ACS or PCI after their first AF diagnosis from 2008/1/1 to 2016/4/1. To identify the presence of AF and ACS, we used the Ninth and Tenth Revisions of the International Classification of Diseases, Clinical Modification (ICD-9-CM and ICD-10-CM, respectively) diagnosis codes (Supplementary Table 1). A patient was defined as having AF if he or she had at least one inpatient/emergency room or two outpatient visits with the associated diagnosis. The diagnosis of AF was also confirmed based on electrocardiogram reports made by cardiovascular (CV) specialists. An ACS event was defined as at least one primary diagnosis of AMI or unstable angina during an inpatient stay or emergency room visit. PCI procedures were identified based on inpatient procedure records, using ICD-9-CM procedure codes and the ICD-10 Procedure Coding System (ICD-10-PCS) (detailed codes are listed in Supplementary Table 1). We defined a new ACS and PCI as no prior ACS event or PCI procedure for at least 1 year to minimize the potential lasting effects of a previous ACS or PCI. The admission for the new ACS or PCI was defined as the index hospitalization. We further excluded patients if they (i) had a prior coronary artery bypass graft (diagnosis and procedure codes are listed in Supplementary Table 1) in the year prior to the index hospitalization; (ii) died during the index hospitalization; (iii) had no follow-up visits; or (iv) did not receive antithrombotic therapy or used only single antiplatelet or anticoagulant treatment at discharge from the index hospitalization.

Exposure

To study the long-term effectiveness and safety outcomes of different antithrombotic regimens, we defined the exposure groups based on medication at discharge from the index hospitalization. The antithrombotic regimens of interest included DAPT, DT, and TT. Anatomical Therapeutic Chemical (ATC) codes and generic names were used to identify drug exposure (a list is provided in Supplementary Table 2). Combination therapy was defined as having at least 3 days of overlap of the individual drugs to ensure a true combination. To account for possible noncompliant behavior, we added a grace period, defined as the addition of 50% of drug supply, fol-

lowing the discontinuation of each drug to assess continuous drug exposure.[11] If the gap between two successive prescriptions was shorter than the grace period, we assumed that the patients were under continuous medication exposure.

Follow-up

The discharge date of the index hospitalization was defined as the index date, and patients were followed until the events of interest, regimen discontinuation or change, loss of follow-up at NTUH, 1 year after ACS or PCI, or the end of the data period, whichever occurred first. To minimize informative censoring bias, 7 days of follow-up for observing bleeding events were added as a latent period when the patients were only followed up until regimen discontinuation or change (i.e. when using the as-treated approach).

Endpoints and definitions

We reviewed the EMRs and used death records, ICD diagnosis codes (Supplementary Table 3), and transfusion records to identify the outcomes. The effectiveness outcome was MACCEs, which included CV death, non-fatal stroke, non-fatal myocardial infarction (MI), and target vessel revascularization (TVR). CV death was defined as death due to MI, heart failure, cardiac arrest, or a cerebrovascular accident including ischemic and hemorrhagic stroke.[12] Patients were defined as having a non-fatal MI or non-fatal stroke if they had a corresponding primary diagnosis from inpatient hospitalization or emergency room visit. An event of TVR was defined as the repetition of revascularization procedures during the first year of follow-up. Safety outcomes of interest were any bleeding and major bleeding using the Platelet Inhibition and Patient Outcomes (PLATO) criteria, which define major bleeding as fatal bleeding, intracranial bleeding, a > 3 g/dL drop in hemoglobin or requiring > 2 units of red blood cell transfusion.[13,14] Any bleeding was defined as major bleeding, any bleeding documented in the medical charts, and any transfusion.

Statistical analysis

The DAPT group was considered to be the reference group, and pairwise comparisons were performed between the DAPT and other regimen (TT and DT) groups. The Student's T-test was used to compare continuous variables, and the chi-square (χ^2) or Fisher's exact test was used to compare categorical variables between two groups. The proportion of missing values in study variables ranged from 1~19% (Supplementary Table 4). With the assumption of missing at random (MAR), multiple imputation was used to handle missing data. Multiple imputation is considered to be the best general method of treating missing data that may provide unbiased results with the least impact of the missing mechanism and proportion.[15,16] Propensity score (PS) methods were applied to mimic randomized controlled trials and avoid selection bias.[17] PS was first estimated for each pairwise comparison using logistic regression modeling, and inverse probability of treatment weighting (IPTW) was then applied by assigning each patient a weight to create a pseudo-population in which the patients' characteristics between treatment groups were balanced. The standardized difference was calculated to assess the balance between any two groups after weighting, and a difference < 0.1 in the score was considered to indicate negligible imbalance.[18]

To account for switching antithrombotic therapies in a real-world setting, we used the as-treated approach in our main analysis. The treatment effect for the time to the first event was estimated using Cox proportional hazards models. The covariates that remained imbalanced after weighting were included in the regression models through stepwise selection (significance level for entering and stay criteria set at 0.1). The strength of the association between exposure and outcome was expressed as the crude incidence rate and adjusted hazard ratio (aHR) with the 95% confidence interval (CI). In patients receiving warfarin, international normalized ratio (INR) observations over the follow-up period were collected. We also conducted 6- and 12-month intention-to-treat (ITT) analysis, which is an approach for following patients until an event has occurred, loss of follow-up, or 6 months or 1 year (depending on the period for outcome analysis) after ACS or PCI, to determine whether the different definitions of censoring (as opposed to the as-treated approach) might have affected the results. Moreover, because the reimbursement duration for prescribing a P_2Y_{12} inhibitor in Taiwan depends on the stent type and clinical condition [3 months for bare-metal stents (BMSs); 6 months for drug-eluting stents

(DESs); 9 months for ACS], we conducted 3- and 6-month as-treated sensitivity analyses to examine the bias associated with potential informative censoring. A p value of < 0.05 was considered to be significantly different. All analyses were conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Description of the study sample

The detailed screening flow chart is illustrated in Figure 1. Among the 900 patients identified with underlying AF and a new ACS or PCI, 719 received antithrombotic therapy at discharge from the index hospitalization. The most commonly prescribed antithrombotic therapy was DAPT (53.3%), followed by single antiplatelet (SAPT) (23.9%), TT (11.1%), DT (9.6%), and a single oral anticoagulant (SOAC) (2.1%). Only patients with DAPT, TT, and DT were included in the analysis (532 patients). We did not include patients who were prescribed with SAPTs and SOACs in further analyses because they tended to have more severe bleeding disorders at baseline or other critical diseases with poor prognoses that confined the use of combined antithrombotic therapy. The average age of the 532 patients was 72.2 [standard deviation (SD) 11.3] years, and 73% were male. Paroxysmal AF was the main type of AF (68.6%). Eighty-five percent of the patients had a CHA_2DS_2-VASc score ≥ 2, and 66.2% had a HAS-BLED score ≥ 3. Approximately half (49.1%) of the subjects were hospitalized for elective PCI, and the other half presented with ACS. Overall,

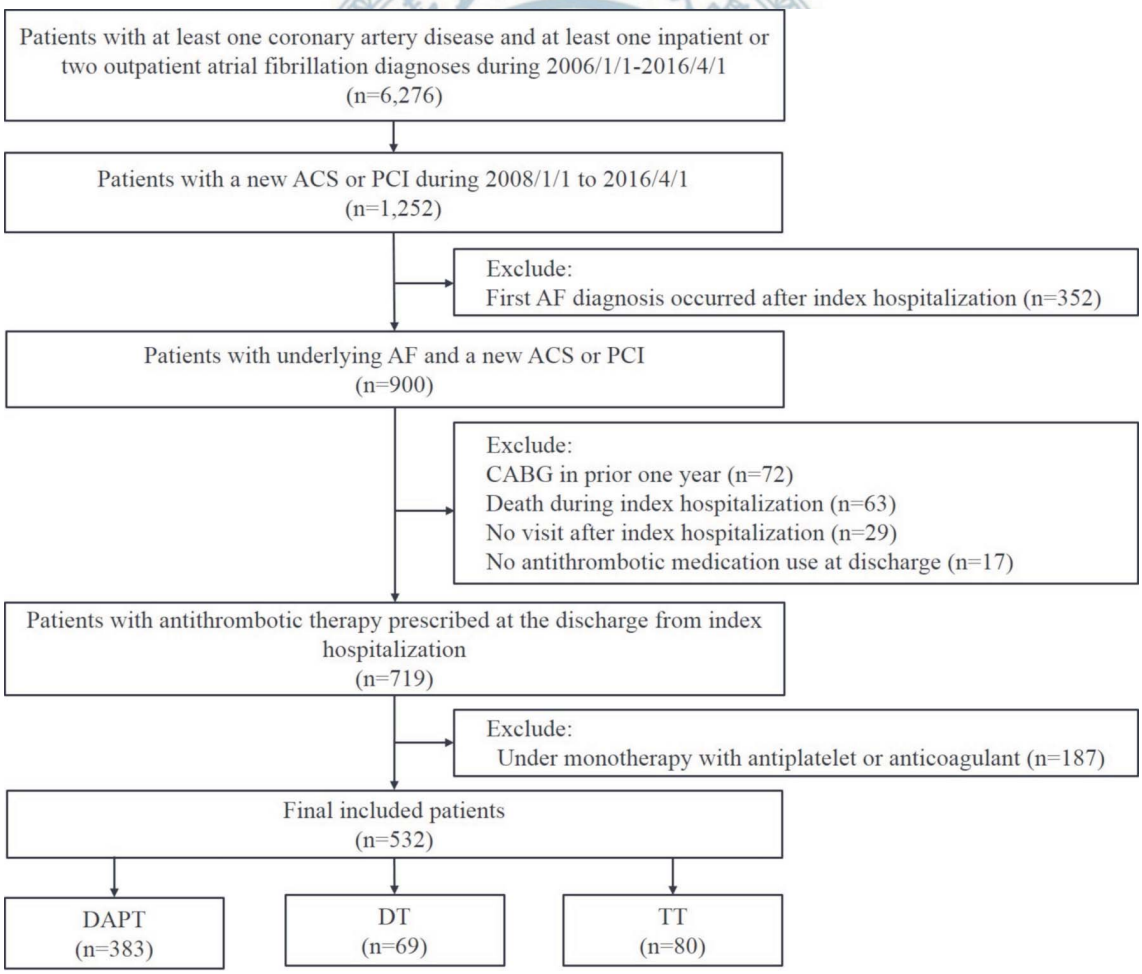

Figure 1. *Patient screening flowchart. Included study patients were grouped based on the antithrombotic therapy received at discharge from the index hospitalization. Only DAPT, DT and TT groups were compared in the subsequent analyses. DAPT, dual antiplatelet therapy; DT, dual therapy; TT, triple therapy.*

60.1% of the patients received DESs. Of the patients receiving DT, 84.1% received an oral anticoagulant (OAC)/P_2Y_{12} inhibitor, and 15.9% were treated with OAC/aspirin. In the patients receiving TT and DT, the anticoagulant of choice was mainly warfarin (TT: 78.8%, and DT: 79.7%) rather than non-vitamin K antagonist oral anticoagulants (NOACs). Details of the antithrombotic regimens are provided in Supplementary Table 5.

Characteristics of the study groups

Compared to the patients receiving DAPT, those receiving TT were more likely to have persistent AF, baseline OAC use, history of stroke or transient ischemic attack (TIA), heart failure, digoxin use, received a radial PCI approach, and were less likely to have received a stent (p values all ≤ 0.01) (Table 1). Most of the DTs were prescribed during 2012-2016. The differences in

Table 1. Comparison of baseline characteristics among treatment groups

	DAPT (n = 383)	TT (n = 80)		DT (n = 69)	
	n (%)	n (%)	p value*	n (%)	p value*
Baseline characteristics					
Age, mean ± SD	71.95 ± 11.22	73.06 ± 10.61	0.42	72.72 ± 12.50	0.61
20-59	56 (14.6)	11 (13.8)	0.40	14 (20.3)	0.10
60-74	157 (41.0)	27 (33.8)		19 (27.5)	
≥ 75	170 (44.4)	42 (52.5)		36 (52.2)	
Male	277 (72.3)	56 (70.0)	0.67	54 (78.3)	0.31
BMI, mean ± SD	25.51 ± 4.05	25.64 ± 3.63	0.80	25.22 ± 3.69	0.58
BMI < 24	128 (36.9)	22 (28.9)	0.28	29 (43.3)	0.58
24 ≤ BMI < 27	99 (28.5)	28 (36.8)		16 (23.9)	
BMI ≥ 27	120 (34.6)	26 (34.2)		22 (32.8)	
Family history of coronary artery disease	158 (48.8)	33 (47.1)	0.81	29 (46.8)	0.77
Current smoker	65 (19.3)	14 (19.7)	0.93	13 (19.4)	0.98
Index year					
2008-2011	178 (46.5)	32 (40.0)	0.29	17 (24.6)	0.001
2012-2016	205 (53.5)	48 (60.0)		62 (89.9)	
Type of AF					
Paroxysmal AF	284 (74.2)	37 (46.3)	< 0.001	31 (44.9)	< 0.001
Persistent or permanent AF	99 (25.8)	43 (53.8)		38 (55.1)	
Prior MI	42 (11.0)	13 (16.3)	0.18	7 (10.1)	0.84
Prior stroke/TIA	63 (16.4)	23 (28.8)	0.01	23 (33.3)	0.001
Prior ICH	5 (1.3)	0 (0.0)	0.60	0 (0.0)	1.00
Prior non-ICH bleeding	59 (15.4)	14 (17.5)	0.64	13 (18.8)	0.47
Prior CABG (at least one year prior to index date)	6 (1.6)	2 (2.5)	0.63	3 (4.4)	0.15
Baseline oral anticoagulant	15 (3.9)	62 (77.5)	< 0.001	41 (59.4)	< 0.001
Baseline transfusion	33 (8.6)	10 (12.5)	0.28	5 (7.3)	0.71
CHA_2DS_2-VASc					
< 2	60 (15.7)	9 (11.3)	0.31	11 (15.9)	0.95
≥ 2	323 (84.3)	71 (88.7)		58 (84.1)	
HAS-BLED					
< 3	123 (32.1)	23 (28.8)	0.56	18 (23.2)	0.08
≥ 3	260 (67.9)	57 (71.3)		51 (76.8)	
Characteristics of index hospitalization					
Duration of index hospitalization, mean ± SD	8.49 ± 10.66	7.91 ± 7.61	0.57	9.94 ± 12.05	0.31
> 6 days	151 (39.4)	39 (48.8)	0.12	32 (46.4)	0.28
≤ 6 days	232 (60.6)	41 (51.3)		37 (53.6)	
Main reason for hospitalization					
STEMI	63 (16.4)	17 (21.3)	0.52	9 (13.0)	0.75
NSTE-ACS	128 (33.4)	23 (28.8)		23 (33.3)	
Elective PCI	192 (50.1)	40 (50.0)		37 (53.6)	

Table 1. Continued

	DAPT (n = 383)	TT (n = 80)		DT (n = 69)	
	n (%)	n (%)	p value*	n (%)	p value*
Coronary/PCI characteristics					
Underwent PCI during index hospitalization	340 (88.8)	72 (90.0)	0.75	58 (84.1)	0.15
Underwent CABG	2 (0.5)	0 (0.0)	1.00	1 (1.5)	0.39
Three vessels involvement	166 (47.7)	25 (35.7)	0.07	22 (36.1)	0.09
Left main disease	43 (12.6)	6 (8.5)	0.33	11 (17.5)	0.30
Type of stent					
No PCI	43 (11.8)	8 (10.3)	0.87	11 (16.7)	0.11
Balloon angioplasty	36 (9.8)	10 (12.8)		11 (16.7)	
BMS	65 (17.8)	13 (16.7)		6 (9.1)	
DES	221 (60.6)	47 (60.3)		38 (57.6)	
Total stent length, mean ± SD	40.60 ± 26.38	31.75 ± 18.86	0.003	43.50 ± 33.11	0.59
Total number of stents, mean ± SD	1.65 ± 0.94	1.37 ± 0.66	0.006	1.91 ± 1.24	0.19
Radial approach	114 (33.5)	38 (52.8)	0.001	22 (38.6)	0.45
Lab/examination data					
Left ventricular ejection fraction					
Normal (50-70%)	228 (74.8)	41 (60.3)	0.06	34 (55.7)	0.01
Borderline (41-49%)	46 (15.1)	16 (23.5)		15 (24.6)	
Low (≤ 40%)	31 (10.2)	11 (16.2)		12 (19.7)	
Hemoglobin (g/dL), mean ± SD	12.80 ± 2.09	13.38 ± 2.25	0.05	13.38 ± 2.12	0.05
Comorbidities					
Anemia	41 (10.7)	7 (8.8)	0.60	2 (2.9)	0.04
Chronic kidney disease	89 (23.2)	17 (21.3)	0.70	16 (23.2)	0.10
Chronic obstructive pulmonary disease	35 (9.1)	12 (15.0)	0.11	4 (5.8)	0.36
Diabetes mellitus	162 (42.3)	40 (50.0)	0.21	24 (34.8)	0.24
Heart failure	105 (27.4)	33 (41.3)	0.01	32 (46.4)	0.002
Hyperlipidemia	181 (47.3)	44 (55.0)	0.21	32 (46.4)	0.89
Hypertension	274 (71.5)	61 (76.3)	0.39	46 (66.7)	0.41
Liver disease	41 (10.7)	5 (6.3)	0.23	10 (14.5)	0.36
Malignancy	29 (7.6)	8 (10.0)	0.47	8 (11.6)	0.26
Peptic ulcer	40 (10.4)	5 (6.3)	0.25	9 (13.0)	0.52
Peripheral arterial occlusive disease	33 (8.6)	10 (12.5)	0.28	5 (7.2)	0.71
Valvular heart disease	14 (3.7)	4 (5.0)	0.53	3 (4.3)	0.73
Concomitant medications					
ACEI/ARB	259 (67.6)	49 (61.3)	0.27	36 (52.2)	0.01
Amiodarone	121 (31.6)	25 (31.3)	0.95	18 (26.1)	0.36
Antiarrhythmic agent, Class 1C	37 (9.7)	9 (11.3)	0.67	5 (7.3)	0.53
Beta blocker	252 (65.8)	52 (65.0)	0.89	47 (68.1)	0.71
Calcium channel blocker	143 (37.3)	35 (43.8)	0.28	24 (34.8)	0.69
Digoxin	39 (10.2)	16 (20.0)	0.01	12 (17.4)	0.08
Glucocorticoid	11 (2.9)	2 (2.5)	1.00	2 (2.9)	1.00
NSAID	13 (3.4)	5 (6.3)	0.21	1 (1.4)	0.71
Proton pump inhibitor	112 (29.2)	18 (22.5)	0.22	15 (21.7)	0.20
Statin	191 (49.9)	47 (58.8)	0.15	30 (43.5)	0.33

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; AF, atrial fibrillation; BMI, body mass index; BMS, bare-metal stents; CABG, coronary artery bypass grafting; DES, drug-eluting stents; ICH, intracerebral hemorrhage; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIA, transient ischemic attack.

* The p values were generated by statistical analyses which used DAPT group as the reference group.

baseline characteristics between the DT and DAPT groups were generally in line with those between the TT and DAPT groups. Persistent AF, baseline OAC use, history of stroke or TIA, and heart failure were more frequent in the DT group (p values all ≤ 0.01).

After multiple imputation and IPTW weighting, the standardized differences between treatment groups were substantially reduced. However, some baseline differences remained significant. Most of the residual differences were small (standardized difference < 0.2), and the main differences were found in baseline OAC use and bleeding risk. The covariates that remained significantly different after PS weighting were selected using the stepwise method and were included in the regression model for further adjustment.

Comparison of clinical outcomes

Of the 532 included patients, MACCEs occurred in 22 (4.1%), and bleeding events occurred in 59 (11.1%). Most of the MACCEs (58.2%) and bleeding events (65.5%) occurred within 6 months after the index hospitalization (Supplementary Table 6). When the main analysis was performed using the as-treated approach, the median follow-up durations for MACCEs were 132.5 days in the DAPT group, 30.5 days in the TT group, and 279.5 days in the DT group. The median follow-up durations for any bleeding were similar to but slightly shorter than those of MACCEs (Table 2). The overall incidence rate of MACCEs was 9.2 per 100 person-years, and the overall incidence rates of any bleeding and major bleeding were 25.6 and 12.7 per 100 person-years, respectively. In addition, the incidence rate of MACCEs was highest in the DAPT group (11.9 per 100 person-years) and lowest in the TT group (no events occurred). In contrast, the incidence rate of any bleeding was highest in the TT group (28.3 per 100 person-years), followed by the DAPT (25.7) and DT (23.6) groups (Table 2). These trends were similar in the 12-month ITT analytic approach (Supplementary Table 7).

Kaplan-Meier curves for MACCEs and any bleeding are presented in Figure 2. After adjusting for baseline differences, there were no significant differences in safety outcomes, either major bleeding or any bleeding, between the patients receiving TT and those receiving DAPT (Table 3). We were unable to compare the effectiveness outcomes with the as-treated approach for the TT group because no MACCEs occurred in these patients during the follow-up period. When an ITT approach was used, no differences in effectiveness outcomes were found between the DAPT and TT groups. The average INR was 1.71 (SD 1.01) among the warfarin users in the TT group.

When comparing DT with DAPT, the risk of any bleeding was significantly lower in the DT group (aHR, 0.20, 95% CI, 0.06-0.75, p = 0.017) after adjusting for baseline differences. However, no difference was observed in major bleeding [aHR 0.21, (0.03-1.20), p = 0.07] or MACCEs [aHR 0.45, (0.10-2.01), p = 0.30] (Table 3). The average INR was 1.86 (SD 0.88) among the warfarin users in the DT group. The results of the sensitivity analyses were generally consistent with the primary analysis.

DISCUSSION

While there is abundant literature on managing patients undergoing PCI or with ACS,[19,20] there is only very

Table 2. Event number and incidence rate using as-treated approach

	DAPT (n = 383)	TT (n = 80)	DT (n = 69)
MACCE number	21	0	1
Median (IQR) follow-up duration	132.5 (13.5-348.5)	30.5 (15.0-143.3)	279.5 (21.5-365.0)
Incidence rate	11.87	0	2.50
Any bleeding number	44	6	9
Median (IQR) follow-up duration	119.0 (13.5-329.3)	25.9 (15.0-143.3)	274.0 (15.0-365.0)
Incidence rate	25.73	28.31	23.57
Major bleeding number	22	4	5
Median (IQR) follow-up duration	148.5 (15.0-359.5)	25.9 (15.0-143.3)	279.5 (21.5-365.0)
Incidence rate	11.98	18.71	12.55

Incidence rates are expressed as event per 100 person-years. Median (IQR) follow-up duration is expressed in days.
IQR, interquartile range.

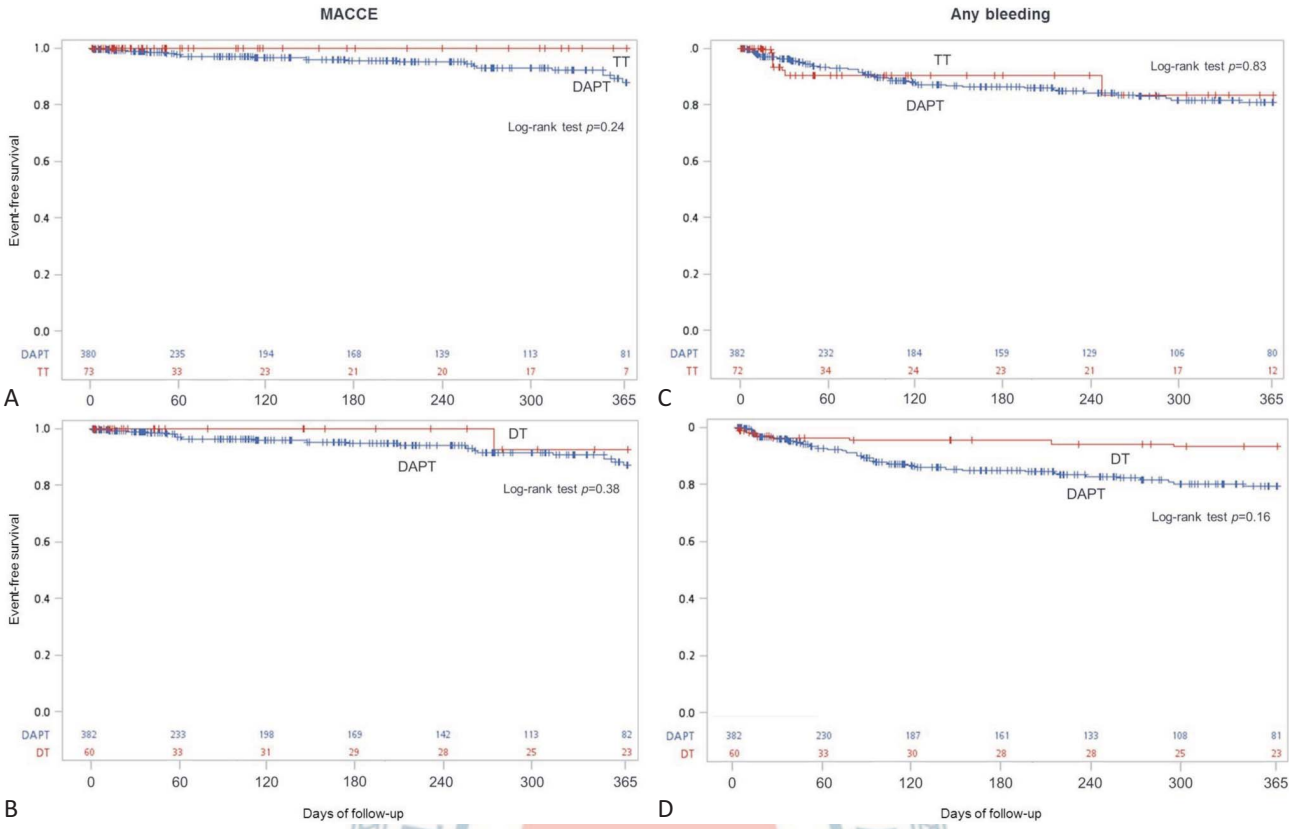

Figure 2. *Kaplan-Meier curves for MACCE and any bleeding. The two figures on the left side (A and B) illustrate MACCE-free survival and the two on the right side (C and D) illustrate bleeding-free survival. Number of patients at risk are listed below each graph. DAPT, dual antiplatelet therapy; DT, dual therapy; TT, triple therapy.*

limited evidence with regards to the clinical outcomes of antithrombotic therapy in patients with coexisting AF. In the present retrospective cohort study, we found that among AF patients presenting with ACS or undergoing a PCI, DT therapy had a comparable risk of MACCEs to DAPT, but the former carried a significantly lower risk of any bleeding. However, the duration of TT therapy was limited, and no differences in major bleeding and any bleeding were observed between the TT and DAPT groups.

Our study also highlights other observations, some of which may reflect important features of patients in Taiwan or other Asian countries. First, only 22.2% of the patients treated with antithrombotic medications received oral anticoagulant therapy to control AF at baseline. Second, after ACS or PCI, DAPT was the most commonly prescribed regimen at discharge (53.3%) among the studied patients rather than TT and DT, which are the two most recommended regimens in clinical guidelines. DAPT is an established treatment after ACS or PCI, and in AF patients with a high CHA_2DS_2-VASc score, adding an OAC should be considered.[3] Although more than 80% of our study patients had a CHA_2DS_2-VASc score of ≥ 2, the use of TT was much less common than observed in Caucasian populations.[21-23] This discrepancy may be due to different concerns of physicians in Asia and Western countries when treating AF patients presenting with ACS or PCI. Compared to other racial/ethnic populations, Asians are more prone to suffer from anticoagulant-related bleeding.[9,10] Our study patients also appeared to have a relatively higher bleeding risk, as indicated by the proportion of patients with a prior bleeding history and a HAS-BLED score ≥ 3 at baseline.

The duration of TT was much shorter in our cohort compared with the results from other Asian studies.[24,25] Among the patients receiving TT, no MACCEs were observed during treatment, and the incidence rate in the DAPT group was the highest. When we used an ITT method as an alternative approach, no differences in effectiveness outcomes were found between the TT and DAPT groups. The finding from the ITT approach, how-

Table 3. Comparison of effectiveness and safety outcomes among treatment groups

	TT versus DAPT			DT versus DAPT		
	Adjusted HR	(95% CI)	p value*	Adjusted HR	(95% CI)	p value*
Primary analysis: as-treated (follow-up up to 1 year)						
MACCE	–[#]	–	–	0.45	(0.10-2.01)	0.30
Any bleeding	0.94	(0.37-2.36)	0.90	0.20	(0.06-0.75)	0.017
Major bleeding	1.53	(0.44-5.27)	0.50	0.21	(0.03-1.20)	0.07
Sensitivity analysis: as-treated (follow-up up to 3 months)						
MACCE	–[#]	–	–	–[#]	–	–
Any bleeding	0.73	(0.22-2.41)	0.60	0.35	(0.08-1.48)	0.15
Major bleeding	2.50	(0.67-9.36)	0.17	0.22	(0.02-1.99)	0.18
Sensitivity analysis: as-treated (follow-up up to 6 months)						
MACCE	–[#]	–	–	–[#]	–	–
Any bleeding	0.75	(0.24-2.28)	0.61	0.23	(0.05-0.98)	0.046
Major bleeding	1.99	(0.59-6.71)	0.27	0.14	(0.01-1.25)	0.08
Sensitivity analysis: ITT (follow-up up to 6 months)						
MACCE	0.42	(0.08-2.09)	0.29	–[#]	–	–
Any bleeding	1.18	(0.59-2.34)	0.65	0.74	(0.29-1.85)	0.51
Major bleeding	1.04	(0.41-2.63)	0.93	1.03	(0.39-2.74)	0.96
Sensitivity analysis: ITT (follow-up up to 1 year)						
MACCE	0.53	(0.18-1.52)	0.24	0.46	(0.13-1.58)	0.21
Any bleeding	1.61	(0.99-2.61)	0.06	0.55	(0.25-1.23)	0.14
Major bleeding	0.90	(0.42-1.94)	0.79	0.87	(0.38-1.98)	0.74

CI, confidence interval; DT, dual therapy; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular event; TT, triple therapy.

MACCE consists of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, and target vessel revascularization. Major bleeding was fatal bleeding, intracranial bleeding, a > 3 g/dL drop in hemoglobin or requiring > 2 units of red blood cell transfusion. Any bleeding was major bleeding and any bleeding documented in medical chart and any transfusion.

* The p values were generated by statistical analyses which used DAPT group as the reference group. [#] Analyses were not performed because no event occurred in one group during the follow-up period.

ever, should be treated with caution because of the time-varying treatment patterns during follow-up, and attributing an event that occurs after therapy discontinuation to that group is not always rational. Although the short duration of TT may limit our ability to study the long-term outcomes, the low utilization was in line with the recommendations and guidelines that for patients with composite indications for TT, limiting the duration of treatment to as short as 1 month is acceptable.[26]

The comparative effectiveness of TT has been questioned in previous studies. A few recent meta-analyses have reported that TT was associated with a significantly higher incidence of all and major bleeding events compared to DT, but with no difference with regards to efficacy endpoints.[27,28] Unlike most studies conducted in Western countries,[29-32] two studies in Asia suggested that TT could prevent more MACCEs than DT or DAPT.[24,33] However, these two studies had a higher percentage of INR observations within the therapeutic range or higher average INR values compared to our study.[24,33] Nonetheless, in the study by Suh et al., the wide range in CI of the odds ratio when comparing TT to DAPT (range from 1.02 to 59.35) could indicate overestimation bias due to using traditional regression adjustments with a small sample size.[34,35] Additional studies should be conducted to confirm whether Asian populations would benefit more from TT.[36] With regards to safety, in contrast to previous Asian studies,[25,37] we did not find a significantly increased bleeding risk for the TT group compared with the DAPT group. Our results, however, should be interpreted with caution given the limited sample size in the TT group. While TT therapy could be used safely in carefully selected patients, especially with a lower target level of anticoagulation, individualized risk stratification should also be incorporated.

Few studies have been published regarding the comparison between DT and DAPT, especially in Asian populations. The findings of our study are consistent

with most studies in that there were no significant differences in MACCEs or major bleeding between the DT and DAPT groups.[21,25,38,39] Interestingly, we found that the risk of any bleeding was significantly lower in the DT group than in the DAPT group, and there was a trend toward a lower risk of major bleeding. One possible explanation for the inconsistent results across studies may be the different intensities of warfarin therapy due to concerns over associated bleeding. In our study, 91.2% of the INR observations were less than 3.0, and 66.5% were less than 2.0. The better risk-benefit profile of DT in our cohort, with a comparable risk of MACCEs but a lower rate of any bleeding compared to DAPT, may be linked to the relatively lower target INR and the absence of aspirin use in the DT users. Future studies are required to confirm the outcomes and further determine the role of DT with low-intensity anticoagulation treatment. In the meantime, consistent with the local consensus and cumulative evidence on the adverse effects of DAPT, the increased bleeding risk in patients receiving DAPT should not be overlooked.[40]

There are several strengths to our study. First, a great deal of clinically important information was collected, including patient social history, bleeding profile, and PCI characteristics. Additionally, a chart review was conducted at an individual patient level to ensure the validity of the outcome measurements and to record outcomes that had occurred in other hospitals. Moreover, efforts were made to control for potential confounders between the treatment groups by PS weighting and multivariate regression adjustments.

Several limitations of this study should be noted. First, uncertainty could exist in the study findings due to its small sample size, which might not provide sufficient power to detect the hypothesized effect. The limited sample size also restricted the number of variables that could be included in the final regression model. Although the stepwise method was used to select variables in that regard, the estimates were similar to those obtained using the full models (data not shown). Second, our data were derived from a single medical center, so generalizing the antithrombotic utilization patterns and outcome findings beyond this level of health care setting warrants caution. In addition, we could not examine whether NOACs provided better outcomes than warfarin because the former were prescribed in only a small proportion of the patients. Clinical trial data have revealed that DT or low-dose TT with NOACs have a lower bleeding rate than TT with warfarin in AF patients undergone PCI.[41,42] Further research is warranted to determine whether these results can be applied to real-world settings and also Asian populations. Finally, although we made substantial efforts in variable collection and adjustments, there could still be residual confounding due to unmeasured variables or inadequate control for the actual tendency of bleeding and thrombus formation.

CONCLUSIONS

In the included AF patients presenting with ACS or a PCI, DAPT was the most commonly prescribed antithrombotic regimen for preventing cardio-cerebrovascular disease at hospital discharge. The effectiveness outcomes were comparable across different antithrombotic strategies, and DT was associated with a lower risk of bleeding compared with DAPT. Future studies are warranted to further determine the role of DT and the comparative effect of NOAC-containing regimens.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Diagnosis and procedure codes used for patient identification

ICD-9-CM codes	Diagnosis/procedure	Category	ICD-10-CM codes/ ICD-10-PCS codes
410.x	Acute myocardial infarction	Acute coronary syndrome	I21.x, I22.x
411.1, 411.8	Unstable angina		I20.0
427.3	Atrial fibrillation and flutter	Atrial fibrillation	I48.x
427.31	Atrial fibrillation		I48.0, I48.1, I48.2, I48.91
427.32	Atrial flutter		I48.3, I48.4, I48.92
36	Operation on vessels of heart		
36.0	Removal of coronary artery obstruction and insertion of stent(s)	PCI	
36.1	Bypass anastomosis for heart revascularization	CABG	
36.2	Heart revascularization by arterial implant	CABG	
	Heart and great vessels, dilation	PCI	027x
	Coronary artery, one artery		0270
	Coronary artery, two arteries		0271
	Coronary artery, three arteries		0272
	Coronary artery, four or more arteries		0273
	Heart and great vessels, bypass	CABG	021x

Supplementary Table 2. ATC codes and generic names of antithrombotic drugs

Generic name	ATC codes
Cyclooxygenase (COX) inhibitor	
Aspirin	B01AC06
Aspirin/dipyridamole	B01AC30
P_2Y_{12} inhibitor	
Clopidogrel	B01AC04
Ticagrelor	B01AC24
Ticlopidine	B01AC05
Oral anticoagulant	
Warfarin	B01AA03
Dabigatran	B01AE07
Rivaroxaban	B01AF01
Apixaban	B01AF02

Supplementary Table 3. Diagnosis codes for outcomes of interest

ICD-9-CM codes	Outcome/diagnosis	ICD-10-CM codes
Effectiveness endpoints		
410.x	Myocardial infarction	I21.x
433.x, 434.x	Ischemic stroke	I63.x, I64.x, G458, G459
Safety endpoints		
430.x-432.x	Intracranial bleeding	I60.x-I62.x, I690-I692, S064-S066

Supplementary Table 4. Proportional of missing data in the study cohort

	Number of missing	%
Patient characteristics		
Height	19	2.6
Weight	48	6.7
BMI	58	8.1
Current smoker	91	12.7
Alcohol use	111	15.4
Family history of coronary artery disease	111	15.4
Three-vessel disease	17	2.4
Left main disease	106	14.7
Coronary/PCI characteristics		
Type of stent	15	2.1
Total number of stents	6	0.8
Total stent length	40	5.6
Radial approach	74	10.3
Lab/examination data		
Left ventricular ejection fraction	125	17.4
Hemoglobin	137	19.1

Supplementary Table 5. Description of antithrombotic regimens in the study cohort

	DAPT (n = 383)	TT (n = 80)	DT (n = 69)
Oral anticoagulant			
Warfarin	-	63 (78.8%)	55 (79.7%)
NOACs	-	17 (21.3%)	14 (20.3%)
Rivaroxaban	-	4*	7[#]
Apixaban	-	4[†]	0
Dabigatran	-	9[‡]	7[§]
Antiplatelet agent			
Aspirin	383 (100%)	80 (100%)	11 (15.9%)
P_2Y_{12} inhibitor	383 (100%)	80 (100%)	58 (84.1%)
Clopidogrel	357	80	53
Ticlopidine	2	0	1
Ticagrelor	24	0	4

* Among these 4 rivaroxaban users, 3 had 10 mg once daily and 1 had missing dosage information. [#] Among these 7 rivaroxaban users, 3 had 15 mg once daily, 1 had 10 mg once daily, and 3 had missing dosage information. [†] Among these 4 apixaban users, 1 had 2.5 mg twice daily, 1 had 5 mg once daily, 1 had apixaban 5 mg twice daily, and 1 had missing dosage information. [‡] Among these 9 dabigatran users, 7 had 110 mg twice daily, 1 had 110 mg once daily, and 1 had missing dosage information. [§] Among these 7 dabigatran users, 2 had 110 mg twice daily, 1 had 150 mg twice daily, and 4 had missing dosage information.

Supplementary Table 6. Time to MACCE and any bleeding event in the one-year follow-up period in all 532 included patients

	MACCE after index hospitalization (n = 55)		Any bleeding after index hospitalization (n = 116)	
Months	n (%)	Cumulative %	n (%)	Cumulative %
$t < 1$	8 (14.6)	14.6	26 (22.4)	22.4
$1 \leq t < 3$	9 (16.4)	30.9	23 (19.8)	42.2
$3 \leq t < 6$	15 (27.3)	58.2	27 (23.3)	65.5
$6 \leq t < 12$	23 (41.8)	100.0	40 (34.5)	100.0

t refers to time to event.

Supplementary Table 7. Event number and incidence rate using 12-month intention-to-treat (ITT) approach

	DAPT (n = 383)	TT (n = 80)	DT (n = 69)
MACCE number	44	8	3
Incidence rate	13.34	11.16	4.42
Any bleeding number	79	24	13
Incidence rate	25.70	38.39	21.67
Major bleeding number	52	4	8
Incidence rate	14.98	18.55	12.51

Incidence rates are expressed as event per 100 person-years.
Median (IQR) follow-up duration is expressed in days.
IQR, interquartile range.