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CORONARY

Prevalence, Management, and Long-Term (6-Year) Outcomes of Atrial Fibrillation Among Patients Receiving Drug-Eluting Coronary Stents

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ABSTRACT

OBJECTIVES This study sought to investigate the incidence, management, and clinical relevance of atrial fibrillation (AF) during and after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) and evaluate outcomes of different antithrombotic strategies.

BACKGROUND Uncertainty exists regarding the optimal antithrombotic strategy in patients with AF who are undergoing PCI with DES.

METHODS Using a consecutive series of 10,027 patients who underwent DES implantation between 2003 and 2011, we evaluated the overall prevalence and clinical impact of AF. In addition, we compared the efficacy and safety of dual antiplatelet therapy (DAPT) (aspirin plus clopidogrel) and triple therapy (DAPT plus warfarin) among patients with AF. The primary outcome was a composite of cardiovascular death, myocardial infarction, or stroke.

RESULTS Overall, 711 (7.1%) patients had a diagnosis of AF at the index PCI. Patients with AF were older, had more comorbid conditions, and more often had a history of strokes; most patients with AF (88.4%) received DAPT rather than triple therapy (10.5%) at discharge. The rate of primary outcome after PCI during the 6-year follow-up period was significantly higher in patients with AF than in those without AF (22.1% vs. 8.0%; $p < 0.001$). This trend was consistent for major bleeding (4.5% vs. 1.5%; $p < 0.001$). After multivariable adjustment, the presence of AF was significantly associated with a higher risk of primary outcome (hazard ratio [HR]: 2.33; 95% confidence interval [CI]: 1.95 to 2.79; $p < 0.001$) and major bleeding (HR: 2.01; 95% CI: 1.32 to 3.06; $p = 0.001$). Among patients with AF, adjusted risk for the primary outcome was similar between the DAPT group and the triple therapy group (HR: 1.01; 95% CI: 0.60 to 1.69; $p = 0.98$), but triple therapy was associated with a significantly higher risk of hemorrhagic stroke (HR: 7.73; 95% CI: 2.14 to 27.91; $p = 0.002$) and major bleeding (HR: 4.48; 95% CI: 1.81 to 11.08; $p = 0.001$).

CONCLUSIONS Among patients receiving DES implantation, AF was not rare and was associated with increased ischemic and bleeding risk. In patients with AF, triple therapy was not associated with decreased ischemic events but was associated with increased bleeding risk compared to DAPT. (J Am Coll Cardiol Intv 2017;10:1075–85)

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

INR = international normalized ratio

MI = myocardial infarction

NOAC = newer oral anticoagulant

OAC = oral anticoagulant therapy

PCI = percutaneous coronary intervention

Atrial fibrillation (AF) is a major public health problem because of its increasing prevalence and strong association with cardiovascular morbidity and mortality (1). For long-term prevention of stroke and systemic embolism, chronic oral anticoagulant therapy (OAC) is recommended for patients with AF at a moderate or high thromboembolic risk. Approximately 5% to 10% of patients undergoing percutaneous coronary intervention (PCI) were reported to have concomitant AF, and long-term OAC was frequently necessary in these patients (2–5). Patients undergoing PCI with stent implantation also require dual antiplatelet therapy (DAPT) (aspirin and $P2Y_{12}$ antagonist), with the goal of reducing the risk of ischemic complications, including stent thrombosis. However, the efficacy and safety of combining OAC with DAPT (triple therapy) in these patients is a topic of debate and a limited evidenced-based data on the optimal antithrombotic strategy is available (6). In addition, the introduction of newer antithrombotic therapies and new stent platforms has raised questions on the optimal antithrombotic treatment regimen for PCI patients who also require OAC because of AF (7).

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Until recently, the prevalence and clinical relevance of AF after PCI with drug-eluting stents (DES) in "real-world" clinical settings had not been fully determined and the optimal antithrombotic therapy for such patients is an emerging clinical problem. The purpose of our study was to: 1) determine the prevalence, treatment, and long-term clinical impact of AF in an unrestricted population who underwent PCI with DES in a "real-world" clinical setting; and 2) compare the relative efficacy and safety of the DAPT and triple therapy in patients with AF using a large cohort of PCI patients receiving DES with long-term follow-up data.

METHODS

STUDY POPULATION AND PROCEDURES. The study population included consecutive patients who underwent PCI with at least 1 DES for stable angina or acute coronary syndromes at Asan Medical Center (Seoul, Korea) from January 2003 to December 2011. At the index hospitalization for PCI, the presence of AF was defined as any previous diagnosis of AF or current AF with documentation of electrocardiogram (the absence of P waves and atrial activity represented by fibrillatory waves and irregular RR intervals). Clinically determined AF patterns were categorized as paroxysmal or sustained forms (persistent or permanent) (8). To reduce the potential confounding bias, patients were excluded if they presented with cardiogenic shock or had documented contraindications to the use of antiplatelet drugs (e.g., a concurrent active bleeding or bleeding diathesis). Patients with an indication for OAC other than AF (e.g., mechanical heart valves, pulmonary embolism, left ventricular mural thrombus) were also excluded. This study was approved by the institutional review board of Asan Medical Center, and all patients provided written informed consent. There was no industry involvement in the design, conduct, or analysis of the study.

PCI was performed according to conventional standards. The choice of the specific type of DES was left to the interventionist's discretion. Periprocedural anticoagulation with heparin was administered according to standard regimens. All patients undergoing PCI received a loading dosage of aspirin (200 mg) and clopidogrel (300 to 600 mg) before or during the intervention. For patients with AF taking chronic warfarin therapy, the international normalized ratio (INR) was tapered to <1.5 during the procedure and warfarin was restarted ≤24 h after DES implantation. After the procedure, patients were prescribed aspirin (100 to 200 mg once daily) indefinitely and clopidogrel (75 mg once daily) for 6 to 12 months. The prolonged use of DAPT was at the discretion of the physician. The new prescription of vitamin K antagonist added to DAPT in patients with AF at discharge was decided by the treating physicians based on several clinical factors and thrombotic and bleeding risk. When warfarin is prescribed, a target INR between 2.0 and 3.0 was recommended.

During the study enrollment period, third-generation $P2Y_{12}$ inhibitors (i.e., prasugrel or ticagrelor) or newer oral anticoagulants (NOACs) were not commercially available in Korea.

ENDPOINTS, DEFINITIONS, AND FOLLOW-UP. The primary outcome was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke (from any cause). The principal secondary outcomes were death (from any cause, cardiovascular or noncardiovascular), MI, stroke (from any cause, ischemic or hemorrhagic), stent thrombosis, repeat revascularization, and bleeding (major or nonmajor).

All deaths were considered to be from cardiovascular causes unless an unequivocal noncardiovascular cause could be established. The diagnosis of acute MI was based on the universal definition of MI (9). Periprocedural or post-procedural elevations of cardiac

enzyme levels were disregarded if ischemic signs or symptoms were absent. Stroke, as detected by the occurrence of a new neurologic deficit, was confirmed by a neurologist and on imaging. Stent thrombosis was defined as the definite occurrence of a thrombotic event, according to the Academic Research Consortium classification (10). Any repeat revascularization was defined as any percutaneous or surgical revascularization, irrespective of whether it was performed on a target or nontarget lesion. Major and nonmajor (minor or minimal) bleedings were assessed in according to the Thrombolysis In Myocardial Infarction criteria (11). All study endpoints were confirmed on the basis of source documentation from medical records and were adjudicated by an independent group of clinicians who were unaware of patient information.

The dataset for the analysis is a part of the ASAN-PCI (ASAN Percutaneous Coronary Intervention) registry, which is a prospective, single-center, observational study (12,13). Baseline and outcome data were prospectively collected by independent research personnel unaware of the study aims and entered into a central database. We systematically reviewed demographics, stroke risk factors, angiographic characteristics, and antithrombotic regimen use during and after PCI. Clinical follow-up after PCI was performed via an office visit or telephone contact at 1, 3, 6, and 12 months and then every 6 or 12 months thereafter. At these visits, data pertaining to patients' clinical status and outcome events were recorded. Adherence to antithrombotic medication and newly prescribed OAC afterward was assessed at each follow-up contact and also verified by pharmacy refill data. For the validation of complete follow-up data, information about vital status was obtained from the National Population Registry of the Korea National Statistical Office with the use of a unique personal identification number.

STATISTICAL ANALYSIS. Baseline characteristics, including patient demographics, risk factors, clinical presentation, cardiac status, anatomical or procedural characteristics, and in-hospital medications, were described for patients with and without AF. Differences between the 2 groups were evaluated by means of Student's *t* test or the Mann-Whitney *U* test for continuous variables and the chi-square or Fisher exact test for categorical variables, as appropriate.

The cumulative incidence of clinical outcomes during follow-up was presented for patients with and without AF. Cumulative probability and event curves were constructed from Kaplan-Meier estimates and compared by use of the log-rank test. To describe the risk associated with the presence of AF, Cox

TABLE 1 Baseline Clinical, Angiographic, and Procedural Characteristics According to AF Status

	Overall PCI Patients (N = 10,027)	AF (n = 711)	Non-AF (n = 9,316)	p Value
Demographics				
Age, yrs	62 (54-69)	68 (61-73.5)	62 (54-68)	<0.001
Male	7,233 (72.0)	523 (73.6)	6,700 (73.6)	0.37
BMI, kg/m^2	24.8 (23.0-26.8)	24.7 (23.0-26.7)	24.9 (23.1-26.8)	0.34
Risk factors and clinical history				
Hypertension	5,652 (56.4)	464 (65.3)	5,188 (55.7)	<0.001
Dyslipidemia	4,513 (45.0)	295 (41.5)	4,218 (45.3)	0.06
Diabetes	2,982 (29.7)	244 (34.3)	2,738 (29.4)	0.006
Prior MI	1,209 (12.1)	99 (13.9)	1,110 (11.9)	0.13
Prior HF	86 (0.9)	21 (3.0)	65 (0.7)	<0.001
Prior CABG	316 (3.2)	38 (5.3)	278 (3.0)	0.001
Prior PCI	1,482 (14.8)	130 (18.3)	1,352 (14.5)	0.007
Prior stroke	593 (5.9)	74 (10.4)	519 (5.6)	<0.001
Peripheral arterial disease	190 (1.9)	30 (4.2)	160 (1.7)	<0.001
Renal failure	259 (2.6)	53 (7.5)	206 (2.2)	<0.001
Ejection fraction	60 (55-64)	59 (51-63)	60 (55-64)	<0.001
Clinical indication for PCI				0.007
Stable angina	5,216 (52.0)	329 (46.3)	4,887 (52.5)	
Unstable angina	3,144 (31.4)	241 (33.9)	2,903 (31.2)	
NSTEMI	1,036 (10.3)	83 (11.7)	953 (10.2)	
STEMI	631 (6.3)	58 (8.2)	573 (6.2)	
Angiographic characteristics				
Extent of disease				<0.001
1-vessel disease	4,191 (41.8)	263 (37.0)	3,928 (42.2)	
2-vessel disease	3,523 (35.1)	241 (33.9)	3,282 (35.2)	
3-vessel disease	2,313 (23.1)	207 (29.1)	2,106 (22.6)	
Vessel treated				
LAD	7,974 (79.5)	558 (78.5)	7,416 (79.6)	0.50
RCA	5,066 (50.5)	401 (56.4)	4,665 (50.1)	0.001
LCX	4,496 (44.8)	365 (51.3)	4,131 (44.3)	<0.001
LM	1,072 (10.7)	81 (11.4)	991 (10.6)	0.57
Venous or arterial graft	162 (1.6)	18 (2.5)	144 (1.5)	0.06
Number of lesions	2.0 ± 1.1	2.2 ± 1.2	2.0 ± 1.1	<0.001
In-stent stenosis	402 (4.2)	42 (6.1)	360 (4.0)	0.009
Procedural characteristics				
Type of DES				0.12
Sirolimus	4,911 (49.0)	379 (53.3)	4,532 (48.6)	
Paclitaxel	1,129 (11.3)	68 (9.6)	1,061 (11.4)	
Zotarolimus	1,759 (17.5)	124 (17.4)	1,524 (17.6)	
Everolimus	1,717 (17.1)	106 (14.9)	1,611 (17.3)	
Others	511 (5.1)	34 (4.8)	477 (5.1)	
Number of stents	2.0 ± 1.1	2.1 ± 1.2	1.9 ± 1.1	0.04
Total stent length	49.1 ± 30.7	48.9 ± 30.5	51.9 ± 33.0	0.06
GP IIb/IIIa antagonists	462 (4.6)	26 (3.7)	436 (4.7)	0.25
Concomitant medication at discharge				
β-blocker	7,377 (73.6)	511 (71.9)	6,866 (73.7)	0.31
ACE inhibitor or ARB	3,225 (32.2)	224 (31.5)	3,001 (32.2)	0.73
Calcium-channel blocker	8,122 (81.0)	566 (79.6)	7,556 (81.1)	0.35
Statin	7,534 (75.1)	494 (69.5)	7,040 (75.6)	<0.001

Values are median (interquartile range), n (%), or mean ± SD.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin-II receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; DES = drug-eluting stent(s); GP = glycoprotein; HF = heart failure; LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main artery; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Baseline Clinical, Angiographic, and Procedural Characteristics Among Patients With AF, According to Antithrombotic Therapy at Discharge

	DAPT* (n = 629)	TT* (n = 75)	p Value
Clinical pattern of AF			<0.001
Sustained (persistent or permanent)†	320 (50.9)	56 (74.7)	
Paroxysmal	309 (49.1)	19 (25.3)	
Demographics			
Age, yrs	68 (61–74)	68 (60–73)	0.61
Male	465 (73.9)	55 (73.3)	1.00
BMI, kg/m^2	24.8 (23.0–26.8)	24.4 (22.9–26.7)	0.49
Risk factors and clinical history			
Hypertension	409 (65.0)	50 (66.7)	0.88
Dyslipidemia	263 (41.8)	31 (41.3)	>0.99
Diabetes	218 (34.7)	23 (30.7)	0.58
Prior MI	91 (14.5)	7 (9.3)	0.30
Prior HF	15 (2.4)	6 (8.0)	0.02
Valvular heart disease	7 (1.1)	11 (14.7)	<0.001
Prior CABG	31 (4.9)	7 (9.3)	0.19
Prior PCI	120 (19.1)	8 (10.7)	0.10
Prior stroke	54 (8.6)	20 (26.7)	<0.001
Peripheral arterial disease	26 (4.1)	4 (5.3)	0.85
Renal failure	45 (7.2)	6 (8.0)	0.98
Ejection fraction	60.0 (52.0–64.0)	56.5 (48.0–62.0)	0.02
Clinical indication for PCI			0.66
Stable angina	296 (47.1)	32 (42.7)	
Unstable angina	210 (33.4)	28 (37.3)	
NSTEMI	74 (11.8)	7 (9.3)	
STEMI	49 (7.8)	8 (10.7)	
Thromboembolic risk			
$CHADS_2$ score	1.39 ± 1.11	1.73 ± 1.48	0.13
CHA_2DS_2-VASc score	2.53 ± 1.58	2.88 ± 1.82	0.16
Low (0)	52 (8.3)	4 (5.3)	0.67
Intermediate (1)	130 (20.7)	16 (21.3)	
High (≥2)	447 (71.1)	55 (73.3)	
Angiographic characteristics			
Extent of disease			0.55
1-vessel disease	229 (36.4)	31 (41.3)	
2-vessel disease	213 (33.9)	26 (34.7)	
3-vessel disease	187 (29.7)	18 (24.0)	
Vessel treated			
LAD	494 (78.5)	58 (77.3)	0.93
RCA	360 (57.2)	37 (49.3)	0.24
LCX	323 (51.4)	39 (52.0)	>0.99
LM	75 (11.9)	6 (8.0)	0.42
Venous or arterial graft	15 (2.4)	3 (4.0)	0.65
Number of lesions	2.2 ± 1.2	2.2 ± 1.1	0.27
In-stent stenosis	39 (6.5)	2 (2.7)	0.30

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proportional hazards models were used. After unadjusted analyses were initially performed, multivariable Cox regression analyses were performed to adjust potential confounders identified by the investigators using a published data search and based on clinical knowledge. These clinically relevant covariates included age, sex, presence or absence of prior heart failure, presence or absence of prior stroke history, presence or absence of peripheral vascular disease, presence or absence of chronic renal failure, and clinical indication for PCI (stable angina, unstable angina, non-ST-segment elevation MI, or ST-segment elevation MI). The proportional-hazards assumption was confirmed by examination of log (- log [survival]) curves and by testing of partial (Schoenfeld) residuals (14), and no relevant violations were found. Baseline variables had <1% missing data. No method was used to impute missing values or adjust the model for the presence of missing data.

To determine whether the type of antithrombotic strategy modified the risk of primary and secondary outcomes among patients who had concomitant AF, patients were categorized into 2 groups, according to the antithrombotic regimen at discharge: 1) DAPT (aspirin plus clopidogrel); and 2) triple therapy (DAPT plus warfarin). Baseline characteristics, thromboembolic risk factors, and the status of antithrombotic regimens during follow-up were compared between the DAPT and triple therapy group. Then, the relationships between the antithrombotic regimens (DAPT vs. triple therapy) and clinical outcomes were investigated with the use of crude and multivariable Cox proportional hazards models. To reduce the impact of treatment selection bias and potential unmeasured confounding in an observational study, we additionally performed rigorous adjustment for differences in baseline characteristics of patients by use of the weighted Cox proportional hazards regression models with the inverse-probability-of-treatment weighting (15).

In this observational research data analysis, to carefully define the population of interest and to minimize data-dredging processes, we pre-specified study objectives, a hypothesis, and a statistical approach using a statistical analysis plan (16). Two-sided p values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with the software R (version 3.2.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENT CHARACTERISTICS. From January 2003 through December 2011, a total of 10,027 patients who received PCI with DES were included in the current analysis. Among them, 711 (7.1%) patients had a previous or concurrent diagnosis of AF at the index hospitalization. Baseline characteristics of the entire population and of the patients according to the presence of AF are shown in Table 1. Compared to patients without AF, those with AF were older, had a

higher risk factor profile, and had more comorbid conditions. Approximately 60% of the patients were treated with first-generation DES (sirolimus- or paclitaxel-eluting stents) and the remaining patients were treated with second-generation DES; there was no difference in DES type between patients with and without AF.

Among the 711 patients with AF, 629 (88.4%) patients were prescribed with DAPT and 75 patients (10.5%) were prescribed with triple therapy at discharge; among the remaining 7 patients, 3 were discharged on single antiplatelet therapy and 4 died before discharge. Baseline characteristics between the DAPT and triple therapy group are shown in Table 2. Compared with patients receiving DAPT, patients receiving triple therapy had a higher proportion of sustained forms (persistent or permanent) of AF and had a higher prevalence of prior heart failure, valvular heart disease, and prior stroke. The mean $CHADS_2$ and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category) scores were nonsignificantly higher in the triple therapy group than in the DAPT group. There were no differences in angiographic and procedural characteristics between the 2 groups. The status of antithrombotic therapy during the follow-up is summarized in Table 3. Adherence to aspirin during the follow-up was similar between the 2 groups. At 1 year, warfarin was being used by 2.2% in the DAPT group and by 75.4% in the triple therapy group. Adherence to clopidogrel was similar up to 1 year; subsequently, discontinuation of clopidogrel was progressively common in the triple therapy group. Overall, in the triple therapy group, the INR values remained at less than the recommended target during the follow-up. In DAPT group, approximately 10% of patients were newly prescribed warfarin during 5-year follow-up after index PCI.

TABLE 2 Continued

	DAPT* (n = 629)	TT* (n = 75)	p Value
Procedural characteristics			
Type of DES			0.38
Sirolimus	334 (53.1)	42 (56.0)	
Paclitaxel	62 (9.9)	5 (6.7)	
Zotarolimus	112 (17.8)	9 (12.0)	
Everolimus	93 (14.8)	13 (17.3)	
Others	28 (4.5)	6 (8.0)	
Number of stents	2.1 ± 1.2	1.9 ± 1.2	0.23
Total stent length	52.2 ± 33.1	49.2 ± 32.4	0.42
GP IIb/IIIa antagonists	31 (4.9)	3 (4.0)	0.94
Concomitant medication at discharge			
β-blocker	450 (71.5)	55 (73.3)	0.85
ACE inhibitor or ARB	198 (31.5)	23 (30.7)	0.99
Calcium-channel blocker	495 (78.7)	66 (88.0)	0.08
Statin	439 (78.7)	48 (64.0)	0.37
Antiarrhythmic drug‡	15 (2.4)	1 (1.3)	0.87
Proton pump inhibitor	51 (8.1)	8 (10.7)	0.59

Values are n (%), median (interquartile range), or mean ± SD. *Dual antiplatelet therapy (DAPT) indicates aspirin and clopidogrel. Triple therapy (TT) indicates aspirin, clopidogrel, and warfarin. †Differentiation between persistent and permanent AF was not considered because diagnosis of these was driven by the attending physician's decision to revert to a sinus rhythm (8). ‡Antiarrhythmic drug indicates use of flecainide or propafenone.

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke/transient ischemic attack; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; other abbreviations as in Table 1.

OUTCOMES. The median follow-up was 6.2 years (interquartile range: 4.2 to 8.5 years). During the follow-up, a total of 319 patients died (127 cardiovascular deaths), 500 patients had an MI, 306 had a stroke, and 875 had at least 1 primary outcome event (i.e., composite of cardiovascular death, nonfatal MI, and nonfatal stroke).

Among patients who underwent PCI with DES, the 6-year rate of primary outcome was significantly higher in patients with AF than in those without AF (22.1% vs. 8.0%, $p < 0.001$) (Table 4, Figure 1). The rate of overall and major bleeding was also higher among AF patients than non-AF patients (9.9% vs. 3.7%, $p < 0.001$; and 4.5% vs. 1.5%, $p < 0.001$, respectively). This trend was consistent for other secondary efficacy and safety outcomes. After multivariable adjustment for traditional risk factors and potential confounders, the presence of AF was significantly associated with a higher long-term risk of ischemic and bleeding events. Overall findings were consistent with propensity-score analysis using the inverse-probability-of-treatment weighting (Online Table 1).

Among patients with AF, the 6-year rate of primary outcome was similar between the DAPT and triple therapy group (20.1% vs. 23.8%; $p = 0.49$) (Table 5, Figure 2). There was a consistent pattern for death or MI. However, the cumulative rate of stroke (in particular, hemorrhagic stroke) and major bleeding was significantly higher in the triple therapy group than in the DAPT group. After multivariable adjustment, the adjusted risk of primary outcome was similar between the 2 antithrombotic groups; however, the adjusted risks of hemorrhagic stroke and major bleeding were significantly higher in the triple therapy group. These findings were almost similar after adjustment of baseline covariates with the inverse-probability-of-treatment weighting (Online Table 2).

In addition, we performed stratified analyses according to the different generation of DES (Online Figures 1 and 2). Consistent with overall findings,

TABLE 3 Status of Antithrombotic Therapy During Follow-Up Among Patients With AF, According to Antithrombotic Therapy at Discharge

	DAPT* (n = 629)	TT* (n = 75)	p Value
Aspirin maintenance			
1 month after the procedure	621/624 (99.5)	74/74 (100)	>0.99
3 months after the procedure	611/618 (98.9)	73/73 (100)	0.77
6 months after the procedure	592/606 (97.7)	69/71 (97.2)	>0.99
1 yr after the procedure	563/586 (96.1)	61/65 (93.8)	0.60
2 yrs after the procedure	491/551 (89.1)	52/57 (91.2)	0.79
3 yrs after the procedure	441/516 (85.5)	39/50 (78.0)	0.23
4 yrs after the procedure	390/449 (86.9)	35/44 (79.5)	0.27
5 yrs after the procedure	340/394 (86.3)	26/34 (76.5)	0.19
Clopidogrel maintenance			
1 month after the procedure	623/624 (99.8)	73/74 (98.6)	0.51
3 months after the procedure	611/618 (98.9)	71/73 (97.3)	0.55
6 months after the procedure	575/606 (94.9)	65/71 (91.5)	0.37
1 yr after the procedure	447/586 (76.3)	49/65 (75.4)	0.99
2 yrs after the procedure	291/551 (52.8)	25/57 (43.9)	0.25
3 yrs after the procedure	238/516 (46.1)	15/50 (30.0)	0.04
4 yrs after the procedure	198/449 (44.1)	12/44 (27.3)	0.05
5 yrs after the procedure	178/394 (45.2)	8/34 (23.5)	0.02
Warfarin maintenance			
1 month after the procedure	0/624 (0)	69/74 (93.2)	<0.001
3 months after the procedure	2/618 (0.3)	59/73 (80.8)	<0.001
6 months after the procedure	3/605 (0.5)	54/71 (76.1)	<0.001
1 yr after the procedure	13/586 (2.2)	49/65 (75.4)	<0.001
2 yrs after the procedure	27/551 (4.9)	37/57 (64.9)	<0.001
3 yrs after the procedure	33/516 (6.4)	29/50 (58.0)	<0.001
4 yrs after the procedure	41/449 (9.4)	24/44 (54.5)	<0.001
5 yrs after the procedure	42/394 (10.7)	18/34 (52.9)	<0.001
INRs			
1 month after the procedure	–	1.70 (1.29-2.35)	–
3 months after the procedure	–	1.94 (1.42-2.64)	–
6 months after the procedure	–	1.58 (1.29-2.15)	–
1 yr after the procedure	–	1.70 (1.19-2.12)	–
2 yrs after the procedure	–	1.88 (1.46-2.28)	–
3 yrs after the procedure	–	1.82 (1.43-2.28)	–
4 yrs after the procedure	–	1.81 (1.38-2.33)	–
5 yrs after the procedure	–	1.65 (1.31-2.24)	–

Values are n/N (%) or median (interquartile range). *DAPT indicates aspirin and clopidogrel. TT indicates aspirin, clopidogrel, and warfarin.

INR = international normalized ratio; other abbreviations as in Tables 1 and 2.

irrespective of DES generation, AF patients were associated with an increased risk of ischemic and patients treated with triple therapy did not have reduced ischemic events but did have increased bleeding complications compared to patients treated with DAPT.

DISCUSSION

The major findings from this long-term (6 years) follow-up of a large cohort study examining the prevalence and clinical impact of AF and comparing the safety and efficacy of different antithrombotic therapies for patients with AF undergoing PCI with DES are that: 1) approximately 7% of patients treated with DES had AF, and the presence of AF was significantly associated with a higher long-term risk of ischemic and bleeding events; 2) despite the guideline recommendation of triple therapy for AF patients undergoing PCI, most patients were discharged on DAPT, reflecting the physician's safety concerns of OAC use with DAPT in real-world practice; and 3) in AF patients, triple therapy was associated with a higher risk of hemorrhagic stroke and major bleeding without a difference in efficacy outcomes compared with DAPT.

Similar to previous studies (2-5), we found that approximately 1 in 10 patients receiving PCI with DES had a prevalent AF and AF patients had more severe comorbidities and more complex coronary artery disease at baseline. In a prognostic viewpoint, considering the chronic nature and impact of AF, very long-term follow-up in our large cohort of PCI patients is clinically important and informative for the treating physicians or patients. The presence of AF was significantly associated with increased risks of major cardiovascular events, death, stroke, and stent thrombosis; this trend has progressively diverged during the long-term follow-up. The strong association of AF with mortality and cardiovascular events was previously reported (5,17,18). We also observed a higher incidence of TIMI major and nonmajor bleeding in patients with AF, confirming previous findings from the earlier studies (5,19,20). Such findings suggest that AF is one of the highest-risk categories within the broad spectrum of future cardiovascular risks among patients undergoing PCI with DES.

The practice guidelines and expert consensus documents recommend triple therapy for high-risk patients with AF who underwent PCI at discharge (7,18,21). However, our study demonstrated that only approximately 10% were treated with triple therapy and this proportion was relatively lower than that in other ethnic or clinical groups (22-24). This disparity might be partly explained by less aggressive clinical guidelines on thromboembolic prevention during our study enrollment period and a relatively low $CHADS_2$ score. In addition, in real-world PCI practice, there have been profound concerns about the excess risk of bleeding complications with triple therapy; therefore, intuitively physicians are likely to underuse OAC add-on DAPT and, if triple therapy used, show a tendency to maintain INR value at a relatively lower range.

Several observational studies have shown conflicting results on the benefit of triple therapy (24-27). Since DES were introduced, aside from several

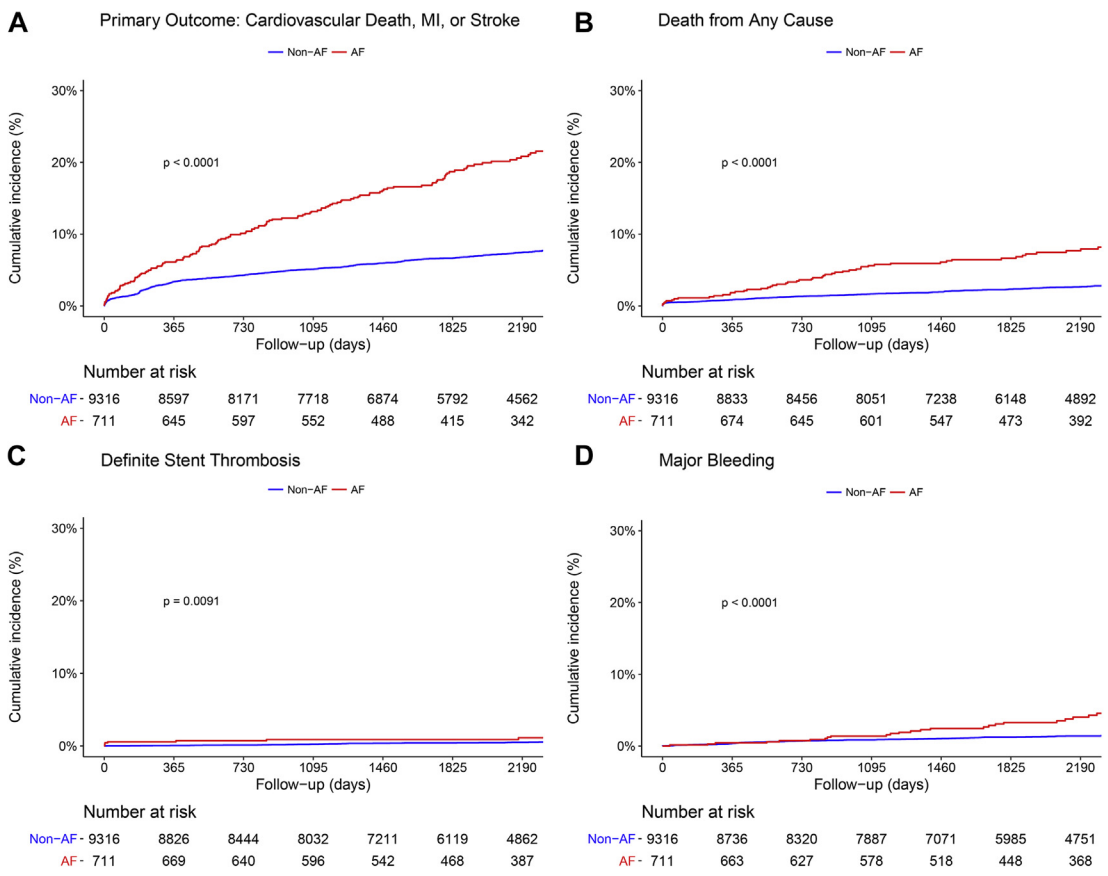
TABLE 4 Outcome Rates at 6 Years and Unadjusted and Adjusted HRs for Clinical Outcomes, According to AF Status

	Total (N = 10,027)	Non-AF (n = 9,316)	AF (n = 711)	Unadjusted HR	p Value	Adjusted HR*	p Value
Primary outcome							
Composite of CV death, MI, or stroke	748 (9.1)	616 (8.0)	132 (22.1)	2.85 (2.40–3.39)	<0.001	2.33 (1.95–2.79)	<0.001
Secondary outcomes							
Death	265 (3.3)	216 (2.9)	49 (8.1)	2.96 (2.23–3.91)	<0.001	1.72 (1.29–2.31)	<0.001
Cardiovascular	109 (1.3)	84 (1.1)	2 (4.2)	3.97 (2.64–5.98)	<0.001	2.09 (1.35–3.22)	<0.001
Noncardiovascular	156 (2.0)	132 (1.9)	24 (4.1)	2.35 (1.59–3.47)	<0.001	1.45 (0.97–2.17)	0.07
MI	433 (5.3)	380 (5.0)	53 (9.0)	1.90 (1.46–2.48)	<0.001	1.83 (1.40–2.39)	<0.001
Stroke	253 (3.2)	185 (2.5)	68 (12.0)	4.64 (3.60–5.99)	<0.001	3.33 (2.54–4.35)	<0.001
Ischemic	182 (2.4)	125 (1.7)	57 (10.1)	5.54 (4.16–7.39)	<0.001	4.00 (2.96–5.42)	<0.001
Hemorrhagic	47 (0.6)	39 (0.6)	8 (1.5)	3.07 (1.59–5.92)	<0.001	2.36 (1.19–4.65)	0.01
Definite stent thrombosis	45 (0.6)	38 (0.6)	7 (1.2)	2.42 (1.19–4.95)	0.01	2.86 (1.37–5.96)	0.005
Repeat revascularization	1,089 (13.5)	994 (13.2)	95 (16.9)	1.24 (1.02–1.51)	0.03	1.35 (1.11–1.64)	0.003
Bleeding	328 (4.2)	274 (3.7)	54 (9.9)	2.53 (1.94–3.30)	<0.001	1.93 (1.47–2.54)	<0.001
Major	133 (1.8)	111 (1.5)	22 (4.5)	2.68 (1.78–4.03)	<0.001	2.01 (1.32–3.06)	0.001
Nonmajor	195 (2.5)	163 (2.2)	32 (5.4)	2.43 (1.71–3.45)	<0.001	1.88 (1.31–2.69)	<0.001

Event rates are shown as Kaplan-Meier estimates, n (%). HRs are for the AF group as compared with the non-AF group. *Models were adjusted for age, sex, the presence or absence of prior HF, the presence or absence of prior stroke history, the presence or absence of peripheral vascular disease, the presence or absence of chronic renal failure, and clinical indication for PCI (stable angina, unstable angina, NSTEMI, or STEMI).

CI = confidence interval; CV = cardiovascular; other abbreviations as in Table 1.

FIGURE 1 Cumulative Incidence for the Primary Outcome and Selected Key Secondary Outcomes, According to the Presence or Absence of AF



Cumulative incidence curves are shown for the **(A)** primary outcome (composite of cardiovascular death, nonfatal myocardial infarction [MI], or nonfatal stroke), **(B)** death from any cause, **(C)** definite stent thrombosis, and **(D)** major bleeding. All p values were calculated with the use of the log-rank test. AF = atrial fibrillation.

TABLE 5 Outcome Rates at 6 Years and Unadjusted and Adjusted HRs for Clinical Outcomes Among Patients With AF, According to Antithrombotic Therapy at Discharge

	Total (N = 704)	DAPT* (n = 629)	TT* (n = 75)	Unadjusted HR	p Value	Adjusted HR†	p Value
Primary endpoint							
Composite of CV death, MI, or stroke	128 (21.7)	112 (20.1)	16 (23.8)	1.19 (0.72–1.98)	0.49	1.01 (0.60–1.69)	0.98
Secondary endpoint							
Death	45 (7.2)	40 (7.1)	5 (7.6)	0.94 (0.38–2.36)	0.90	0.99 (0.38–2.59)	0.99
Cardiovascular	21 (3.4)	18 (3.3)	3 (4.4)	1.27 (0.38–4.24)	0.70	1.27 (0.36–4.46)	0.71
Noncardiovascular	24 (3.9)	22 (3.9)	2 (3.4)	0.68 (0.16–2.85)	0.59	0.75 (0.17–3.31)	0.70
MI	53 (9.0)	40 (8.9)	3 (4.9)	0.44 (0.14–1.40)	0.16	0.38 (0.12–1.23)	0.11
Stroke	68 (12.0)	56 (10.4)	12 (18.3)	1.88 (1.04–3.42)	0.04	1.66 (0.89–3.10)	0.11
Ischemic	57 (10.1)	50 (9.3)	7 (9.8)	1.33 (0.64–2.79)	0.45	1.13 (0.53–2.44)	0.75
Hemorrhagic	8 (1.5)	4 (0.7)	4 (7.9)	5.74 (1.68–19.63)	0.005	7.73 (2.14–27.91)	0.002
Definite stent thrombosis	7 (1.2)	7 (1.3)	0 (0.0)	NA	NA	NA	NA
Repeat revascularization	95 (17.0)	85 (15.8)	10 (15.6)	0.88 (0.46–1.69)	0.71	0.81 (0.42–1.57)	0.53
Bleeding	53 (10.0)	43 (8.4)	10 (16.6)	2.03 (1.06–3.88)	0.03	2.17 (1.11–4.24)	0.02
Major	21 (4.5)	14 (3.1)	7 (13.0)	3.49 (1.47–8.26)	0.005	4.48 (1.81–11.08)	0.001
Nonmajor	32 (5.8)	29 (5.5)	3 (4.2)	1.17 (0.41–3.29)	0.77	1.12 (0.39–3.23)	0.83

Event rates are shown as Kaplan-Meier estimates, n (%). HRs are for the TT group as compared with the DAPT group. *DAPT indicates aspirin and clopidogrel. TT indicates aspirin, clopidogrel, and warfarin. †Models were adjusted for age, sex, the presence or absence of prior HF, the presence or absence of prior stroke history, the presence or absence of peripheral vascular disease, the presence or absence of chronic renal failure, and clinical indication for PCI (stable angina, unstable angina, NSTEMI, or STEMI).

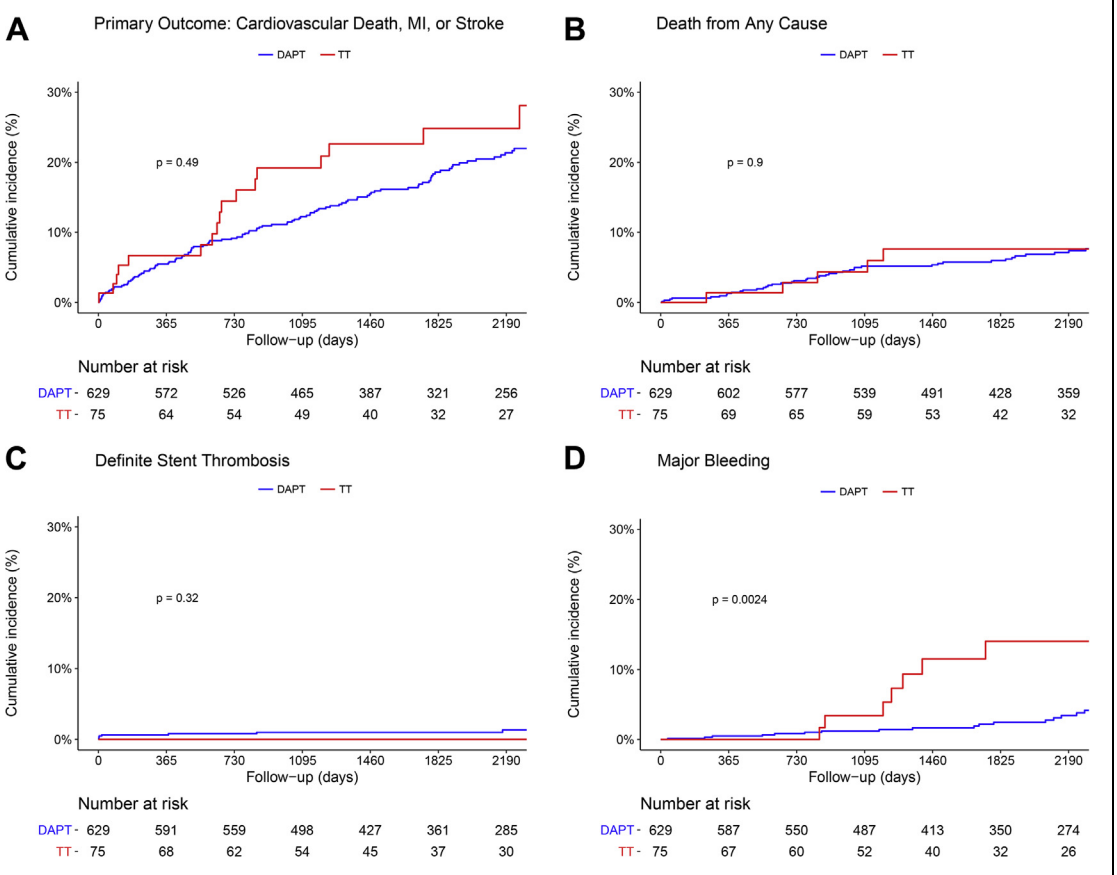
NA = not available; other abbreviations as in Tables 1, 2, and 4.

registries of patients with AF, the best available evidence is based on a few randomized trials with limited number of patients. The WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial showed that among patients undergoing PCI who were taking OAC, clopidogrel alone (compared with DAPT) was associated with a significant reduction of bleeding complications and no increase of thrombotic events (28). By contrast, in the ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen-Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting) trial, there was no difference in ischemic and bleeding events between shorter (6 weeks) and longer (6 months) durations of DAPT in patients on warfarin receiving DES (29). Hence, because evidence-based data on the optimal antithrombotic treatment regimen are still limited, this critical issue warrants further investigation to determine the best clinical management, which would ideally be confirmed through sufficiently large randomized trials with long-term follow-up.

Interestingly, in the present study, there was no case of stent thrombosis with triple anticoagulant therapy, which might fit well with the reduction in stent thrombosis with triple therapy with rivaroxaban in the ATLAS-ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 51) trial (30). However, because of the low number of events, the related findings may be due to chance and should be interpreted with caution.

The potential role of NOAC added to antiplatelet therapy for patients with AF undergoing PCI is actively under investigation. Recent results from the PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) trial provide novel evidence to support the use of a NOAC in patients with AF undergoing PCI with placement of stents; rivaroxaban-based treatment strategies demonstrate improved safety and similar efficacy outcomes compared with triple therapy including a vitamin K antagonist (31). However, there was a lack of confidence in the efficacy endpoint benefit with NOAC. Subsequent clinical trials, such the REDUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; NCT02164864, dabigatran), AUGUSTUS

FIGURE 2 Cumulative Incidence for the Primary Outcome and Selected Key Secondary Outcomes Among Patients With AF, According to Use of Dual Versus Triple Antithrombotic Therapy



Cumulative incidence curves are shown for the **(A)** primary outcome (composite of cardiovascular death, nonfatal MI, or nonfatal stroke), **(B)** death from any cause, **(C)** definite stent thrombosis, and **(D)** major bleeding. All p values were calculated with the use of the log-rank test. Dual antiplatelet therapy (DAPT) indicates aspirin and clopidogrel and triple therapy (TT) indicates aspirin, clopidogrel, and warfarin; other abbreviations as in Figure 1.

(A Study of Apixaban to Vitamin K Antagonist for the Prevention of Stroke or Systemic Embolism and Bleeding in Patients With Non-valvular Atrial Fibrillation and Acute Coronary Syndrome/Percutaneous Coronary Intervention; NCT02415400, apixaban), and ENTRUST-AF-PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; NCT02866175, edoxaban), will provide further insights regarding the role of NOAC for patients with an indication for OAC who have undergone PCI.

STUDY LIMITATIONS. The potential limitations of this study warrant discussion. As an observational cohort study, residual confounding cannot be completely excluded. Therefore, our results should be considered as hypothesis generating. And, because individual decision making in antithrombotic therapy among AF patients was at the physicians' discretion, the comparative findings may have been influenced by unmeasured confounders. Because NOAC and newer antiplatelet drugs (i.e., prasugrel and ticagrelor) was not commercially available during the study period, we could not evaluate the efficacy and safety of these drugs. Although our study did not find any differences in efficacy outcomes of patients with triple therapy compared with DAPT, this should not encourage physicians to disregard the use of OAC. Current observational findings might be vulnerable to selection bias and the potential possibility of study underpower to detect clinically meaningful difference.

CONCLUSIONS

In our large cohort of patients who underwent DES implantation, AF was not rare and was significantly associated with an increased risk of ischemic and bleeding events. For patients with AF, most were discharged on DAPT without oral anticoagulants. Compared with DAPT, triple therapy was associated with substantially higher risks of hemorrhagic stroke and major bleeding without reduction of thromboembolic events. However, due to the small number of events, these findings should be confirmed or refuted through large clinical trials. Further large randomized trials will provide the valuable clinical information to guide the best therapeutic strategy for patients with AF who are undergoing PCI with DES, according to the risk spectrum of expected thromboembolic and bleeding events.

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PERSPECTIVES

WHAT IS KNOWN? AF is not rare in patients undergoing PCI with DES, and long-term anticoagulation therapy was necessary in most of these patients. However, the clinical relevance and the optimal antithrombotic strategy for AF in patients treated with DES is still undetermined.

WHAT IS NEW? This analysis of 10,027 patients who underwent DES implantation demonstrated that prevalence of AF was not rare (approximately 7%) and the presence of AF was associated with increased ischemic and bleeding risk. Most of patients with AF (88%) were discharge on DAPT and 11% on the triple therapy (DAPT plus warfarin); however, the triple therapy was not associated with decreased ischemic events, but was associated with increased bleeding risk.

WHAT IS NEXT? Further researches are required to determine how the NOACs and new antiplatelet drugs might change the practice pattern for management of AF patients receiving PCI with DES.

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KEY WORDS anticoagulation, antiplatelet therapy, atrial fibrillation, drug-eluting stents

APPENDIX For supplemental tables and figures, please see the online version of this article.