Effect of atrial fibrillation in Asian patients undergoing percutaneous coronary intervention with drug-eluting stents for stable coronary artery disease

Results from a Korean nationwide study

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Abstract

Although the prevalence of atrial fibrillation (AF) and percutaneous coronary intervention (PCI) are increasing in Asia, there is a paucity of data concerning the effect of AF in Asian patients undergoing PCI with drug-eluting stents (DESs). Furthermore, the majority of previous studies investigating the effect of AF on prognosis following PCI have exclusively evaluated patients with myocardial infarction (MI). We aimed to evaluate the effect of AF on clinical outcomes of Asian patients undergoing PCI with DES for coronary artery disease (CAD) excluding acute MI.

From national health insurance claims data in South Korea, a total of 45,288 patients aged 18 years or older without a known history of CAD, who underwent PCI with DES for the diagnosis of CAD excluding acute MI between 2011 and 2015, were enrolled. Based on the presence or absence of a history of AF at baseline, patients were categorized into the AF group (n = 1715, 3.8%) and no-AF group (n = 43,573, 96.2%). Outcomes including all-cause death, the composite outcome of all-cause death/MI/coronary revascularization, and stroke were compared between 2 groups using a propensity-score-matched analysis.

After propensity-score matching, 1709 matched pairs were obtained. During the follow-up period (mean, 2.2 years), the incidence of all-cause death (hazard ratio [HR] 1.117, 95% confidence interval [CI] 0.885–1.411, $P = .35$) and the composite outcome of all-cause death/MI/coronary revascularization (HR 1.004, 95% CI 0.846–1.192, $P = .97$) were not significantly different between 2 groups. However, the incidence of stroke was significantly increased in the AF group (HR 1.983, 95% CI 1.474–2.667, $P < .001$).

In Asian patients undergoing PCI for stable CAD, a history of AF was not associated with mortality, but was associated with increased risk of stroke.

Abbreviations: AF = atrial fibrillation, CAD = coronary artery disease, CI = confidence interval, DES = drug-eluting stent, HIRA = Health Insurance Review & Assessment Service, HR = hazard ratio, MI = myocardial infarction, NHI = National Health Insurance, NOAC = nonvitamin K antagonist oral anticoagulant, PCI = percutaneous coronary intervention.

Keywords: atrial fibrillation, coronary artery disease, drug-eluting stent, percutaneous coronary intervention

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1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia requiring treatment and is associated with an increased risk of death and cardiovascular disease.[1,2] Coronary artery disease (CAD) is the leading cause of death worldwide[3] and patients with CAD often have coexistent AF because they share common risk factors including aging, hypertension, and congestive heart failure. In the United States, approximately 12% of patients undergoing percutaneous coronary intervention (PCI) were reported to have concomitant AF.[4] In addition, AF is known to be associated with increased mortality in patients undergoing PCI.[5–7] Although prevalence rates of AF and PCI have progressively increased in Asia,[8,9] the clinical effect of AF on Asian patients with PCI is uncertain. Furthermore, the majority of previous studies investigating the effect of AF on prognosis following PCI have exclusively evaluated patients with myocardial infarction (MI).[10–12] Therefore, little is known about the prevalence and effect of AF in Asian patients who underwent PCI without MI. This study sought to evaluate the clinical effect of AF on clinical outcomes of Korean patients treated with drug-eluting stents (DESs) for CAD excluding MI.

2. Methods

2.1. Data sources

In South Korea, all healthcare providers have had to join the national health insurance (NHI) system on a fee-for-service basis. The Health Insurance Review & Assessment Service (HIRA) is a quasi-governmental organization that systematically reviews medical fees to minimize the risk of redundant and unnecessary medical services. Consequently, all NHI claims are reviewed by the HIRA.[13] For this study, data from 2011 to 2015 claims records of the HIRA were used. International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes were used. In addition, specific information about the procedure, devices, and drugs were identified by codes from the HIRA database.[13] The study protocol was approved by the Institutional Review Board at Ulsan University Hospital, Ulsan, Korea (approval number: 2017-01-026). Patient information was anonymized and deidentified prior to analysis. The requirement for informed consent was waived because of the anonymity of the patients and the nonintrusive nature of the study.

2.2. Study population

From the claims database of the HIRA between July 2011 and June 2015, we identified patients aged 18 years and older who had undergone PCI (M6551, M6552, M6561-4, M6571, and M6572) with DES (J5083XXX) for the diagnosis of CAD (ICD-10 codes I20.X-I25.X). Patients with at least 6 months of eligibility prior to the index day were selected. Specifically, patients with an index procedure for the diagnosis of acute MI (I21.X-I22.X) were excluded to focus on stable CAD. We excluded patients if the HIRA database indicated that they had a previous history of CAD (ICD-10 codes I20.X-25.X) within 6 months of the index day to ensure that only patients with the 1st episode of stable CAD were included. Additionally, patients who died during hospitalization after the index procedure were excluded to create a more homogeneous population by reducing patient-related confounding factors. We also excluded patients with insufficient data in the HIRA database. Then, patients were categorized into the AF group and no-AF group based on the presence of a history of AF (ICD-10 codes I48, I48.0, and I48.1) within 6 months prior to the index day.

2.3. Study variables

The ICD-10 codes were used to identify comorbid conditions such as hypertension, diabetes, diabetes with chronic complications, dyslipidemia, congestive heart failure, valvular disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, moderate-to-severe liver disease, renal disease, cancer, rheumatic disease, AF, and arrhythmia other than AF.[14] The Charlson comorbidity index, $CHADS_2$ score, and CHA_2DS_2-VASc score were obtained from the ICD-10 codes.[14] In the HIRA database, all prescribed medications were recorded with rigorous accuracy. Patients were considered to have hypertension and dyslipidemia if antihypertensive and antidyslipidemic drugs were identified. Furthermore, we identified medications used, such as antiplatelet agents, statins, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, antiarrhythmic drugs, and oral anticoagulants.[13]

2.4. Clinical outcomes

The primary endpoint of this study was all-cause death. Clinical outcomes such as the composite of all-cause death/MI/coronary revascularization and stroke were also evaluated. In patients with multiple clinical events, the 1st event was considered to be the component of the composite outcome. Death was identified by all in- and out-patient claims that indicated death. MI was defined using the hospital discharge databases of the HIRA (ICD-10 codes I21.X-22.X). Coronary revascularizations in the HIRA database were identified using the procedure codes of PCI (M6551, M6552, M6561-4, M6571, and M6572) and coronary artery bypass surgery (O1641, O1642, O1647, OA641, OA642, and OA647). Stroke (ischemic or hemorrhagic) was identified using the hospital discharge databases of the HIRA (ICD-10 codes I60.X-169.X). In this study, for the evaluation of clinical outcomes, the HIRA database was used until July 2016.[13]

2.5. Statistical analysis

All baseline patient characteristics and comorbid conditions were summarized as mean ± standard deviation or frequency (percentage) for continuous or categorical variables, respectively. Categorical data were compared using Chi-squared or Fisher exact tests. Continuous variables with a normal distribution were compared using the Student t test, and those without a normal distribution were compared using the Mann–Whitney U test. Cumulative incidence rates for clinical outcomes were estimated using the Kaplan–Meier method. We compared the cumulative incidence rates between the AF and No-AF groups using the log-rank test. We used the propensity-score matching method to reduce potential confounding factors in demographics and comorbid conditions between the AF and no-AF groups. The propensity scores were derived nonparametrically using the variables of age, gender, hypertension, diabetes, diabetes with chronic complications, dyslipidemia, congestive heart failure, arrhythmia other than AF, valvular disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, renal disease, cancer, rheumatic disease, Charlson comorbidity index, CHA_2DS_2-VASc score, number of stents, and medications at discharge, which were documented in the baseline characteristics. Propensity-score matching was performed by nearest neighbor matching with caliper size 0.2 multiplied by the standard deviation for linearly transformed propensity scores (logit-transformation). The balance of covariates was measured by their standardized differences in means. All of the standardized differences for the baseline variables were <0.2 (20%), so that all pretreatment variables were balanced. Furthermore, we conducted the paired t test or the McNemar test for continuous or categorical variables to evaluate the covariate balance between the 2 matched groups. In the propensity-score-matched cohort, the risks of clinical events were compared via the Cox proportional hazard regression model with robust standard errors accounting for the clustering of matched pairs. Results of the Cox proportional hazard model were presented as the hazard ratio (HR) and 95% confidence interval (CI). Analyses were performed using R software, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and R package of MatchIt[15] was used for the matching analyses. All reported P-values are 2-sided, and P-values <.05 were considered to indicate statistical significance.

3. Results

From July 2011 through June 2015, a total of 187,863 patients aged 18 years and older undergoing PCI with DES for CAD were identified from the claims database of HIRA. Among them,
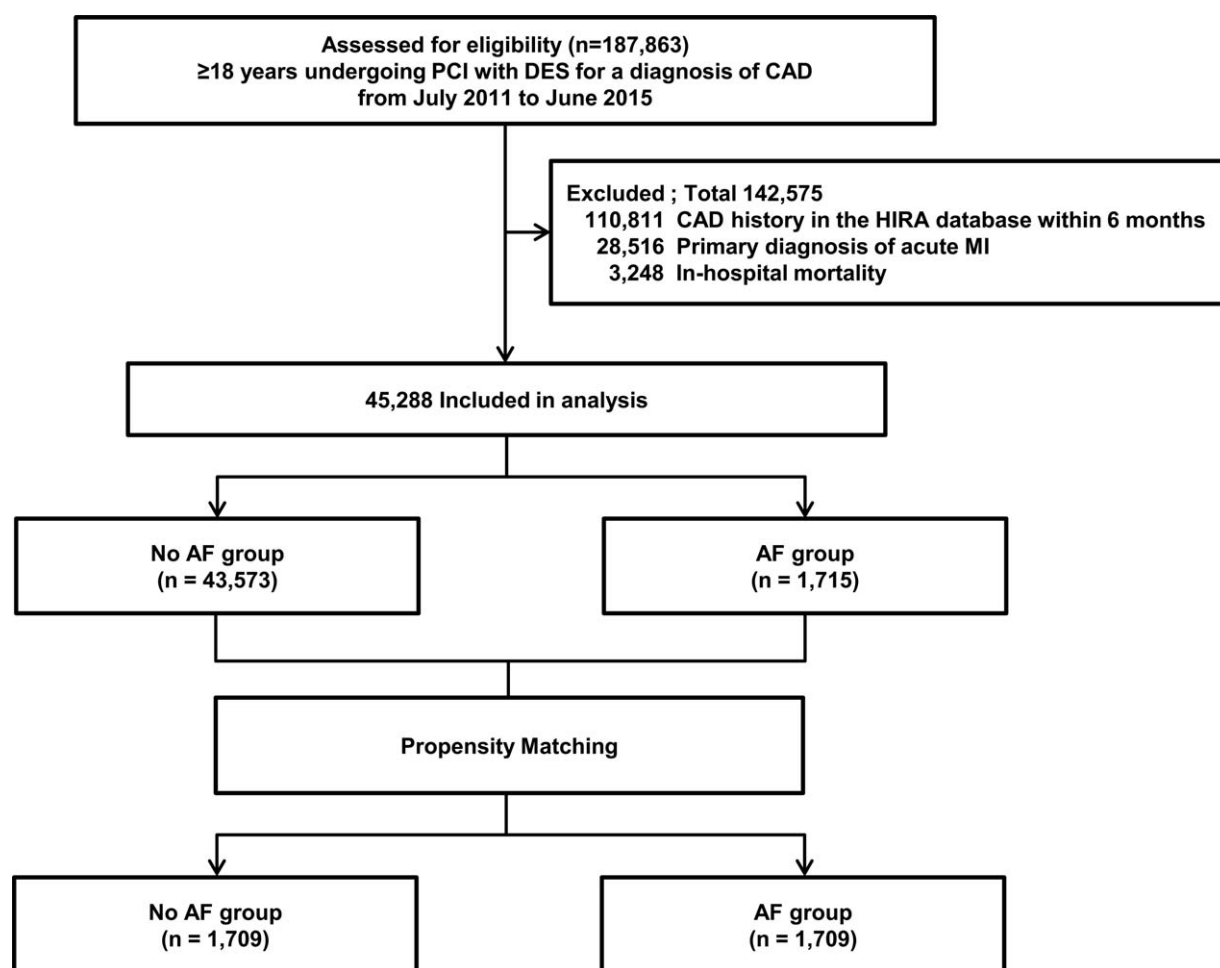
Figure 1. Diagrammatic representation of the study. AF = atrial fibrillation, CAD = coronary artery disease, DES = drug-eluting stents, HIRA = the Health Insurance Review & Assessment Service, MI = myocardial infarction, PCI = percutaneous coronary intervention.

45,288 patients met the eligibility criteria and were selected as the study population (Fig. 1). The mean age of study participants was 64.9 ± 11.4 years and 30,171 (66.6%) were men. At baseline (within 6 months prior to index day), 1715 patients (3.8%) had a history of AF. Table 1 shows the baseline characteristics of the study population based on the presence of a baseline AF history. Patients with a history of AF (AF group, n = 1715) were older and had more comorbidities (hypertension, diabetes, dyslipidemia, congestive heart failure, arrhythmia other than AF, valvular disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, renal disease, and cancer) than those without a history of AF (no-AF group, n = 43,573). At discharge, the AF group was prescribed more oral anticoagulant and antiarrhythmic drug and less antiplatelet agents and statins than the no-AF group.

During a mean follow-up of 2.2 years, the AF group was more likely to have all-cause death, the composite of all-cause death/ MI/coronary revascularization, and stroke than the no-AF group (P-value for all <.05). Figure 2 shows the unadjusted cumulative incidence rates for clinical outcomes of the 2 groups.

After propensity-score matching, there were 1709 patients matched pairs (Fig. 1). In the matched cohort, there were no other significant differences between the AF and no-AF groups for any of the covariates (Table 2). During a mean follow-up of 2.2 years,

the incidence of the primary endpoint, defined as all-cause death, was not different between the AF and no-AF groups (HR of AF group: 1.117; 95% CI: 0.885–1.411; P = .352). In addition, the occurrence of the composite endpoint of all-cause death/MI/ coronary revascularization did not differ between the 2 groups (HR of AF group: 1.004; 95% CI: 0.846–1.192; P = .965). However, incidence of stroke was significantly higher in the AF group (HR of AF group: 1.983; 95% CI: 1.474–2.667; P < .001) (Table 3).

4. Discussion

This study aimed to evaluate the effect of AF on clinical outcomes of Asian patients undergoing PCI with DES. The major findings of the present study using NHI claims data in South Korea are as follows: in patients undergoing PCI with DES for CAD excluding MI, a history of AF was not associated with an increased risk of all-cause death and the composite of all-cause death/MI/coronary revascularization; however, a history of AF increased the risk of stroke by 2-fold.

In this study, the prevalence of a history of AF was 3.8% among patients undergoing PCI with DES for CAD excluding MI. Although the prevalence of AF in our study is lower than that reported in previous studies, most previous studies included

Baseline characteristics of patients undergoing percutaneous coronary intervention with drug-eluting stents for coronary artery disease excluding myocardial infarction according to the presence of a history of atrial fibrillation.

Characteristics	Overall (n = 45,288)		
	No-AF (n = 43,573)	AF (n = 1715)	P-value
Demographic characteristics			
Age, y	64.7 ± 11.4	70.7 ± 9.5	<.001
Male, %	29084 (66.7)	1087 (63.4)	.004
Enrolled number, %			.75
July 2011 to June 2012	9790 (22.5)	376 (21.9)	
July 2012 to June 2013	10484 (24.1)	424 (24.7)	
July 2013 to June 2014	11535 (26.4)	440 (25.7)	
July 2014 to June 2015	11764 (27.0)	475 (27.7)	
Comorbid conditions (%)			
Hypertension	27019 (62.0)	1594 (92.9)	<.001
Diabetes	16127 (37.0)	815 (47.5)	<.001
Diabetes with chronic complications*	133 (0.3)	4 (0.2)	.82
Dyslipidemia	19632 (45.1)	1050 (61.2)	<.001
Congestive heart failure	2731 (6.3)	473 (27.6)	<.001
Arrhythmia other than AF	2101 (4.8)	304 (17.7)	<.001
Valvular disease	153 (0.4)	64 (3.7)	<.001
Peripheral vascular disease	5073 (11.6)	243 (14.2)	.002
Cerebrovascular disease	5994 (13.8)	456 (26.6)	<.001
Chronic pulmonary disease	7135 (16.4)	438 (25.5)	<.001
Moderate to severe liver disease	25 (0.1)	0 (0.0)	>.99
Renal disease	2217 (5.1)	163 (9.5)	<.001
Cancer	1190 (2.7)	72 (4.2)	.001
Rheumatic disease	88 (0.2)	6 (0.3)	.17
Charlson comorbidity index	1.38 ± 1.40	2.17 ± 1.59	<.001
CHADS$_2$ score	1.37 ± 1.10	2.23 ± 1.07	<.001
CHA$_2$DS$_2$-VASc score	2.26 ± 1.58	3.39 ± 1.45	<.001
Number of drug-eluting stents			.29
1	29634 (68)	1191 (69.4)	
2	10058 (23.1)	368 (21.5)	
≥3	3881 (8.9)	156 (9.1)	
Medication at discharge (%)			
Antiplatelet agent	43288 (99.3)	1692 (98.7)	.002
Beta-blocker	28027 (64.3)	1112 (64.8)	.68
ACEI/ARB	27401 (62.9)	1116 (65.1)	.07
Statin	38144 (87.5)	1365 (79.6)	<.001
OAC	893 (2.1)	581 (33.9)	<.001
Warfarin	869 (2.0)	571 (33.3)	<.001
NOAC	24 (0.1)	10 (0.6)	<.001
Antiarrhythmic drug	882 (2.0)	339 (19.8)	<.001
Ic	127 (0.3)	130 (7.6)	<.001
III	755 (1.7)	209 (12.2)	<.001
Dual antiplatelet agent	38737 (88.9)	1520 (88.6)	.72
OAC with single antiplatelet agent	33 (0.1)	32 (1.9)	<.001
OAC with dual antiplatelet agent	805 (1.8)	527 (30.7)	<.001

Data are expressed as number (%) and mean ± standard deviation.
ACEI = angiotensin-converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin II receptor blocker, NOAC = nonvitamin K antagonist oral anticoagulant, OAC = oral anticoagulant.
* Including diabetic nephropathy, retinopathy, or neuropathy.

patients with acute MI.[4,5,7,10] On the contrary, the prevalence of AF in this study is consistent with a previous study conducted on patients with stable CAD.[16] In addition, consistent with previous studies, our results showed that patients with a history of AF were older and had more comorbidities than those without a history of AF.[4,7]

Several previous studies demonstrated that AF in patients with CAD increased the risk of in-hospital and long-term mortality. In

the thrombolytic era, Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) study showed that AF in patients with acute MI independently predicts increased 30-day mortality.[17] Even in the PCI era, several studies showed that AF increases the risk of in-hospital and long-term mortality in patients undergoing PCI.[4,6,7] Unlike previous studies, however, we did not observe an increase in mortality among patients with a history of AF (HR: 1.117; 95% CI: 0.885–1.411; P = .352). Furthermore, the composite outcome of all-cause death/MI/coronary revascularization did not differ between patients with and without a history of AF (HR: 1.004, 95% CI: 0.846–1.192, P = .965). This might be explained by the difference in the definition of AF and in the study population compared to previous studies. Most previous studies defined AF to include new-onset AF during hospitalization.[5,7,10,17] When the definition of AF was confined to baseline AF, not new-onset AF during hospitalization, AF did not have a prognostic implication. The Osaka Acute Coronary Insufficiency Study (OACIS)[10] reported the clinical outcomes from 2475 patients with AMI treated with PCI according to presence of AF, and revealed that AF was an independent predictor of 1-year mortality (HR: 1.64; 95% CI: 1.05–2.55; P = .03). When AF was stratified according to the time of AF (AF at admission versus new-onset AF during hospitalization), however, the prognostic effect of AF was different. New-onset AF during hospitalization was independently associated with 1-year mortality (HR: 3.04; 95% CI: 1.24–7.48), but AF at admission was not associated with 1-year mortality (HR: 1.87; 95% CI: 0.45–7.57). Pilgrim et al[7] also reported the composite outcome of all-cause mortality, MI, stroke, and major bleeding in patients undergoing PCI with DES according to AF. Although new-onset AF was associated with an increased risk of adverse outcome (HR: 2.04; 95% CI: 1.33–3.01; P < .0001), preexisting AF did not have a statistically significant association with adverse outcomes (HR: 1.43; 95% CI: 0.98–2.07; P = .062). The above findings suggest that new-onset AF might be a consequence of the acute MI and it could be a manifestation of acute hemodynamic compromise due to the acute MI. However, preexisting AF (history of AF) was not associated with acute MI, as opposed to new-onset AF during hospitalization, and it was not associated with increased risk of mortality. Furthermore, our study population included patients with CAD but no MI. Sutton et al[4] showed that in-hospital mortality was increased in patients with a history of AF. However, they could not identify a statistically significant association between AF and in-hospital mortality in the stable angina subgroup (odds ratio: 7.33; 95% CI: 0.19–282.27). Therefore, we suggest that a history of AF, unlike new-onset AF, might not be associated with an increased risk of mortality in patients undergoing PCI for CAD excluding MI. In our study, the risk of MI and coronary revascularization was not different between the AF and no-AF groups. This is consistent with previous studies in the DES era.[4,6,7]

Stroke is the most common and most devastating complication of AF. Although there are conflicting evidences, CAD is suggested as a risk factor of stroke in patients with AF.[18–20] Recent study also suggested that CAD is an independent risk factor for ischemic stroke among patients with AF (adjusted incidence rate ratios: 1.29; 95% CI: 1.08–1.53).[21] In the Framingham study, coronary heart disease with AF was associated with an increased risk of stroke by 2-fold in men and nearly 5-fold in women compared with those without AF.[22] In addition, intracranial hemorrhage is increased in patients with AF due to the use of antithrombotic and anticoagulant medication.[23] Previous study
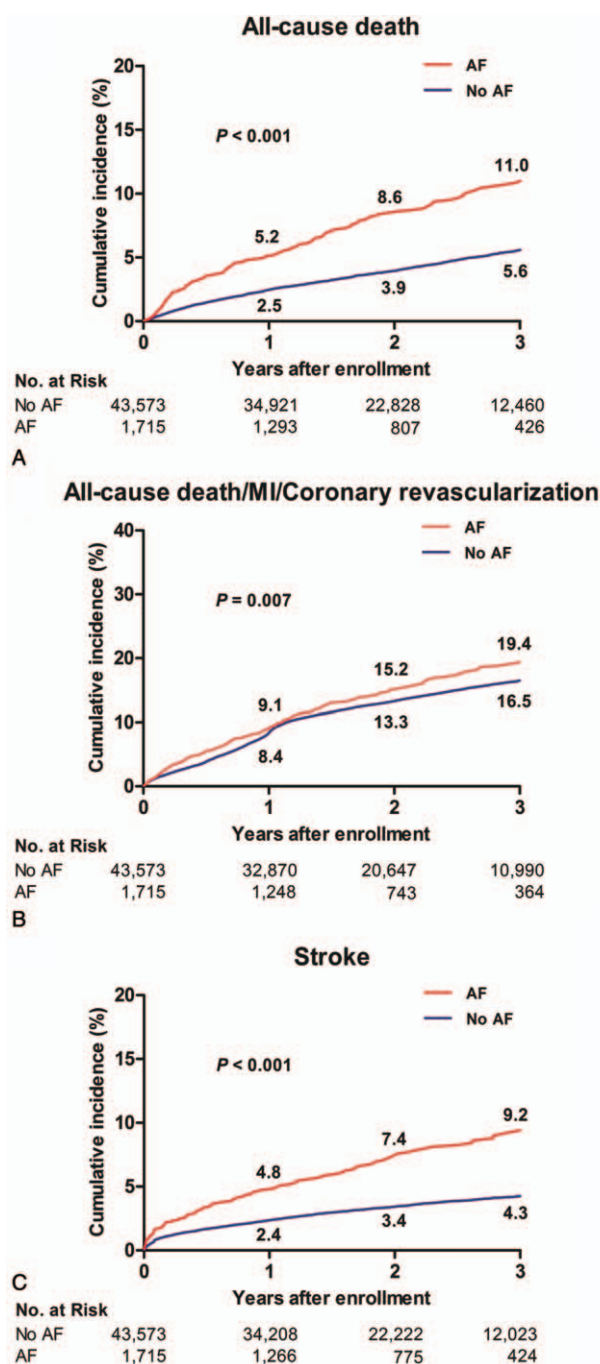
Figure 2. Unadjusted cumulative incidence rates for clinical outcomes in the AF and no-AF groups - Cumulative incidence curves are shown for (A) all-cause death, (B) the composite outcome (all-cause death/MI/coronary revascularization), and (C) stroke. The numbers in each figure represent the cumulative incidence rates at each time point. All *P*-values were calculated with the use of the log-rank test. AF = atrial fibrillation, MI = myocardial infarction.

regarding the long-term effect of AF in patients undergoing DES reported that AF is associated with an increased risk of ischemic stroke and intracranial bleeding.[7] Consistent with previous studies, we found that AF is associated with 2-fold increased risk of stroke (ischemic or hemorrhagic). Recent studies reported that nonvitamin K antagonist oral anticoagulants (NOACs) reduced the risk of intracranial hemorrhage without loss of antithrom-

Table 2

Baseline characteristics of the propensity-score-matched patients according to the presence of a history of atrial fibrillation.

Characteristics	Propensity-score matched (n = 3418)	
	No-AF (n = 1709)	AF (n = 1709)
Demographic characteristics		
Age, y	70.7 ± 9.9	70.7 ± 9.5
Male, %	1064 (62.3)	1083 (63.4)
Clinical history, %		
Hypertension	1582 (92.6)	1588 (92.9)
Diabetes	833 (48.8)	811 (47.5)
Diabetes with chronic complications*	3 (0.2)	4 (0.2)
Dyslipidemia	1018 (59.6)	1045 (61.1)
Congestive heart failure	470 (27.5)	467 (27.3)
Arrhythmia other than AF	287 (16.8)	300 (17.6)
Valvular disease	43 (2.5)	59 (3.5)
Peripheral vascular disease	236 (13.8)	242 (14.2)
Cerebrovascular disease	436 (25.5)	453 (26.5)
Chronic pulmonary disease	448 (26.2)	435 (25.5)
Renal disease	156 (9.1)	161 (9.4)
Cancer	68 (4.0)	72 (4.2)
Rheumatic disease	7 (0.4)	6 (0.4)
Charlson comorbidity index	2.15 ± 1.59	2.16 ± 1.58
CHA_2DS_2-VASc score	3.39 ± 1.49	3.38 ± 1.45
Number of drug-eluting stents	1.40 ± 0.65	1.40 ± 0.67
Medication at discharge, %		
Antiplatelet agent	1690 (98.9)	1686 (98.7)
Beta-blocker	1118 (65.5)	1108 (64.8)
ACEI/ARB	1123 (65.7)	1111 (65.0)
Statin	1385 (81.1)	1363 (79.8)

Data are expressed as number (%) and mean ± standard deviation.
ACEI = angiotensin-converting enzyme inhibitor, AF = atrial fibrillation, ARB = angiotensin ll receptor blocker.
* Including diabetic nephropathy, retinopathy, or neuropathy.

boembolic effect compare to warfarin.[24–27] In particular, NOACs were more beneficial for Asian patients, who are prone to intracranial hemorrhage when treated with warfarin, compared to non-Asian patients.[28,29] In our study, the use of NOACs was limited (<1%) because they were not covered by NHI during the study period. With increased use of NOACs in South Korea, stroke (especially hemorrhagic stroke) could be reduced in this population. However, further clinical studies are needed to confirm this expectation.

This study has several limitations. First, this was a retrospective, observational study. Although we rigorously adjusted for

Table 3

Propensity-score-matched clinical outcomes of patients undergoing percutaneous coronary intervention with drug-eluting stents for coronary artery disease excluding myocardial infarction based on the presence of a history of atrial fibrillation.

Propensity-score-matched analysis	AF compared with no-AF	
	Hazard ratio (95% CI)	*P*-value
All-cause death	1.117 (0.885–1.411)	.35
Death/MI/coronary revascularization	1.004 (0.846–1.192)	.97
MI	0.724 (0.344–1.524)	.40
Coronary revascularization	0.886 (0.684–1.146)	.36
Stroke	1.983 (1.474–2.667)	<.001

AF = atrial fibrillation, CI = confidence interval, MI = myocardial infarction.

baseline covariates using propensity-score matching, there are inherent limitations of a nonrandomized study. Second, this study was based on administrative data from the HIRA in South Korea. Similar to previous studies using administrative databases, we had no clinical data or test findings of the patients. Thus, our findings might be limited by uncertainties in unmeasured confounding variables that may affect patient management.[30] Third, although we used a database from a quasi-governmental organization, there is the possibility that these data did not fully reflect patient outcomes. Additionally, we did not specify the cause of death. Finally, the present study included only the Korean population, and this may limit the applicability of our findings to other countries. However, considering the paucity of data concerning Asian populations, we believe that our study may have clinical implications.

In conclusion, this large nationwide study suggested that AF does not affect all-cause mortality and the composite outcome of all-cause death/MI/coronary revascularization in Asian patients undergoing PCI with DES for stable CAD. However, AF increases the risk of stroke by 2-fold. Further prospective clinical trials are needed to confirm these findings.

Author contributions

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