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**Antithrombotic Therapy in Patients with Atrial Fibrillation after Percutaneous  
Coronary Intervention during 2-year Follow-up, From a Nationwide Population Study**

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**Abstract**

Patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) are recommended to receive oral anticoagulants (OAC) and concomitant antiplatelet agents followed by OAC monotherapy continued beyond a year after PCI. However, long-term prescription patterns of antithrombotic therapy in real-world clinical practice were not fully investigated. From the National Health Insurance Service database of Korea, we obtained records of patients with AF who underwent PCI between 2009 and 2013. Patients without repeated PCI or death within 2 years following the procedure were included. Prescription records of antithrombotic therapy including anticoagulants and antiplatelet agents were reviewed at 3-month intervals after discharge. We investigated 8,891 patients. At discharge, 76.1% of the patients received dual antiplatelet therapy (DAPT) and only 17.1% received OAC. Although the proportion of patients receiving DAPT gradually decreased, >70% of patients received only antiplatelet agents (DAPT or single antiplatelet therapy [SAPT]) a year after PCI. During the 2-year follow-up, the proportion of patients receiving OAC remained <20%, and only 1.5% of the patients received OAC monotherapy a year after PCI. Female sex, previous myocardial infarction, peripheral vascular disease, and prescription of DAPT at discharge were associated with under-prescription of OAC a year after PCI. In conclusion, a significant proportion (76%) of patients with AF undergoing PCI were not prescribed OAC at discharge despite the high risk of stroke contrary to the current guidelines. Most patients continued to receive antiplatelet agents without OAC beyond the 1-year time-point after PCI.

**Keywords**

Atrial fibrillation, percutaneous coronary intervention, antiplatelet therapy, antithrombotic therapy

Oral anticoagulants (OAC) are essential for stroke prevention in atrial fibrillation (AF).<sup>1, 2</sup> Approximately 5–15% of patients with AF undergo percutaneous coronary intervention (PCI) with coronary stent implantation during their lifetime, which requires dual antiplatelet therapy (DAPT). Current guidelines recommend combination antithrombotic therapy with anticoagulants and antiplatelets for patients with AF after PCI.<sup>3, 4</sup> Generally, the treatment comprises triple therapy with OAC and DAPT for the initial 1–6 months followed by dual therapy of OAC and an antiplatelet agent up to 12 months, and then subsequent OAC monotherapy for life-long anticoagulation. Nevertheless, previous studies have reported undertreatment with OAC in patients with AF<sup>5-7</sup> and those undergoing PCI.<sup>8-10</sup> However, limited data are available regarding long-term trends of antithrombotic therapy for patients with AF after PCI in real-world clinical practice. We investigated the 2-year trends of antithrombotic therapy in patients with AF undergoing PCI, using the Korean National Health Insurance database.

## Methods

Data pertaining to the study population were obtained from the National Health Insurance Service claims database, which comprises inpatient and outpatient medical records, diagnostic codes, and claims for procedures and medication prescriptions.<sup>11, 12</sup> The definitions of AF and comorbidities were validated in previous studies.<sup>13-15</sup> Patients with diagnostic codes for AF based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes I480–I484 and I489 during hospitalization or at  $\geq 2$  outpatient clinics were diagnosed with AF. Those with diagnostic codes for mitral stenosis (I50, I52, and I59) or mechanical heart valves (Z952–Z954) were excluded. Procedure codes

for PCI (M6561, M6562, M6563, and M6564) were used to identify PCI events. Definitions of comorbidities are summarized in **Supplementary Table 1**. Hypertension and diabetes mellitus were defined based on diagnostic codes along with prescription claims for at least a single antihypertensive or antidiabetic drug, respectively. Congestive heart failure, stroke or systemic thromboembolism, myocardial infarction (MI), peripheral artery disease (PAD), and intracranial hemorrhage (ICH) were defined based on ICD-10-CM codes. CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were calculated for each patient to assess individual stroke risk.<sup>16</sup>

We included patients with non-valvular AF who underwent PCI between January 2009 and December 2013. Patients who died or underwent repeated PCI during the 2-year follow-up after the index PCI were excluded. We included only those with complete 2-year prescription records for antithrombotics after the index PCI. Eventually, medical records of 8,891 patients were assessed for antithrombotic usage.

We retrieved inpatient and outpatient prescription records (at 3-month intervals) of patients reporting antithrombotic usage including aspirin, clopidogrel, vitamin K antagonists (VKAs), and non-VKA oral anticoagulants (NOACs) from the time of the index PCI until the 2-year follow-up time point. Patients were categorized as those without treatment, those receiving single antiplatelet therapy (SAPT, aspirin or clopidogrel), DAPT (aspirin and clopidogrel), OAC monotherapy (VKAs or NOACs), and OAC with antiplatelet agents (SAPT or DAPT). Edoxaban was introduced in Korea after 2016; thus, it was not included in the NOAC group in our analysis. Also, new generation P2Y<sub>12</sub> inhibitors including prasugrel and ticagrelor were not included because they were not widely available in Korea during the study period.

After categorizing patients based on the antithrombotic regimens at every 3-month



interval, 2-year temporal trends in prescription patterns were analyzed. To identify clinical factors that were independently associated with OAC use a year after PCI, multivariate logistic regression analysis was used after classifying the study population based on OAC prescriptions a year after PCI. This study was exempt from review by the Seoul National University Hospital Institutional Review Board (1706-160-863). Statistical significance was set at 2-tailed p values of  $<0.05$ . Statistical analysis was performed using the SAS software version 9.3 (SAS Institute, Cary, NC, USA).

## Results

Of the total study population, 1,684 patients (18.9%) received OAC a year after PCI (OAC group). **Table 1** shows the baseline characteristics of those with or without OAC a year after PCI. The OAC prescription rate was significantly higher in the OAC group than non-OAC group (68.2% vs. 7.8%,  $p<0.001$ ). The DAPT prescription rate in the OAC group was significantly lower than that in the non-OAC group (42.8% vs. 92.4%,  $p<0.001$ ).

After PCI, 76.1% of patients were prescribed DAPT at discharge whereas only 17.1% had OAC (**Figure 1**). Among those prescribed OAC at discharge, most patients received triple therapy (88.3%,  $n=1,343$ ). During a year of follow-up, the proportion of patients receiving DAPT decreased from 76.1% to 45.9%, and that of patients receiving OAC decreased from 17.1% to 15.2%. Notably, the proportion of patients receiving triple therapy also decreased from 15.1% to 5.1%. A year after PCI, 73.1% of the total study population received only antiplatelet agents (SAPT or DAPT) without OAC. In the OAC group, only 9.9% of the patients were prescribed OAC monotherapy and 90.1% continued to receive combination antithrombotic regimens comprising SAPT (56.6%) or DAPT (33.5%) (**Figure**

2). The OAC prescription rate remained <20% throughout the follow-up.

Old age ( $\geq 65$  years), a history of heart failure, stroke, or systemic thromboembolism, and prescription of OAC at discharge were associated with a higher OAC prescription rate a year after PCI (**Figure 3**). Female sex, a history of MI or PAD, and prescription of DAPT without oral anticoagulation at discharge were associated with the underuse of OAC a year after PCI.

## Discussion

Despite the recommendations of the current guidelines,<sup>3,4</sup> our study shows that most patients with AF (76.1%) did not receive anticoagulation therapy after PCI, and triple therapy was used in only 15.1% of patients. Several studies have reported under-prescription of triple therapy after PCI in patients with AF. In the CRUSADE registry, among the 1,648 patients with AF and non-ST segment elevation MI, only 27% were prescribed triple therapy after PCI.<sup>8</sup> Lamberts et al. reported a population-based study of 12,165 Danish patients and observed that 15% of patients with AF received triple therapy at discharge.<sup>9</sup> Similarly, a recent report analyzing data from an Asian registry showed that only 10% of patients with AF were prescribed triple therapy after PCI.<sup>17</sup>

The discrepancy between the guidelines and real-world practice with respect to antithrombotic therapy after PCI could be attributed to the following: (1) DAPT after PCI is essential to avoid the risk of stent thrombosis.<sup>18</sup> Thus, physicians tend to prioritize DAPT instead of oral anticoagulants after PCI. Interestingly, the treatment pattern of maintaining prolonged DAPT was also found in patients on anticoagulation as 33.5% of them still received triple therapy at a year after PCI; and (2) higher bleeding risks such as intracranial

hemorrhage following anticoagulation therapy in the Asian population may also discourage physicians to prescribe.<sup>19, 20</sup>

During the 2-year follow-up, the proportion of patients receiving DAPT decreased over time. Notably, <20% of patients received OAC throughout the study period, although anticoagulation was clinically indicated in >95% of the non-OAC group a year after PCI. These results are contrary to current guidelines that recommend life-long OAC monotherapy beyond the 1-year time point after PCI.<sup>3, 4</sup> Choi et al. reported that among 629 patients with AF who underwent PCI and were prescribed DAPT, 96.1% and 76.3% continued aspirin and clopidogrel, respectively a year after PCI; however, the OAC prescription rate was significantly low throughout the follow-up (0.5%, 2.2%, and 4.9% at 6 months, 1, and 2 years, respectively).<sup>17</sup>

Lamberts et al. have reported prescription patterns of antithrombotics in 8,700 patients with AF and stable CAD defined as 12 months from an acute coronary event and showed that 62.7% patients (n=5,457) received only antiplatelet agents (SAPT or DAPT). The risk of all-cause death, coronary death, MI, and systemic thromboembolism in these patients was higher than that in patients who received OAC monotherapy.<sup>21</sup> The prescription rate of DAPT a year after PCI was higher in our study (45.9% vs. 20.3%), which could be attributed to the difference in the proportion of patients with AF who underwent PCI (100% vs. 32.5%). We also observed that a history of cardiovascular disease including MI or PAD and the prescription rate of DAPT at discharge were independently associated with the underutilization of OAC a year after PCI. This result suggests that patients with AF in whom long-term antiplatelet therapy is clinically indicated are at an even higher risk of prolonged undertreatment with OAC. AF and concomitant CAD or PAD is associated with a

significantly high risk of adverse cardiovascular events; thus, optimal antithrombotic treatment (including OAC) is extremely important in these patients.<sup>22</sup>

Current guidelines recommend life-long OAC monotherapy after the intensive phase of combination antithrombotic treatment.<sup>3,4</sup> Our study showed that a year after PCI, 33.3% of all patients receiving OAC continued to be prescribed triple therapy and only 9.9% were prescribed OAC monotherapy, which concurs with a previous report.<sup>17</sup> Recently, the OAC-ALONE trial compared the use of OAC alone with a combination of OAC and SAPT and evaluated the efficacy and safety of OAC monotherapy in patients with concomitant AF and stable CAD beyond a year after coronary stenting.<sup>23</sup> Although no significant intergroup differences were observed in primary outcomes, the study was under-powered, and the results were inconclusive. Further prospective randomized trials are warranted to conclusively determine the optimal antithrombotic therapy regimen beyond a year after PCI in patients with AF.

The limitations of our study are as follows: (1) Information regarding medication compliance among patients was unavailable in our study, which may affect the actual proportion of patients receiving different antithrombotic regimens. (2) Information regarding the bleeding risk factors in individual patients including a history of bleeding events or laboratory data such as time in therapeutic range in patients using VKAs were not included for analysis. Also, data on bleeding events observed during the 2-year follow-up were not included in the current analysis. (3) Data regarding the complexity of coronary lesions and the PCI procedure were also not included in our study because detailed information on coronary angiography, procedural records, and laboratory results is unavailable in the claims database. (4) Long-term efficacy and safety outcomes between groups receiving different

antithrombotics were not included in this study. Further studies are needed to evaluate the prognostic effect of various combinations of antithrombotic therapies in patients with AF undergoing PCI.

In summary, a significant proportion (76%) of patients with AF undergoing PCI were not prescribed OAC therapy at discharge despite the high risk of stroke contrary to the current guidelines. Most of these patients continued to receive antiplatelet agents without OAC beyond the 1-year time point after PCI.

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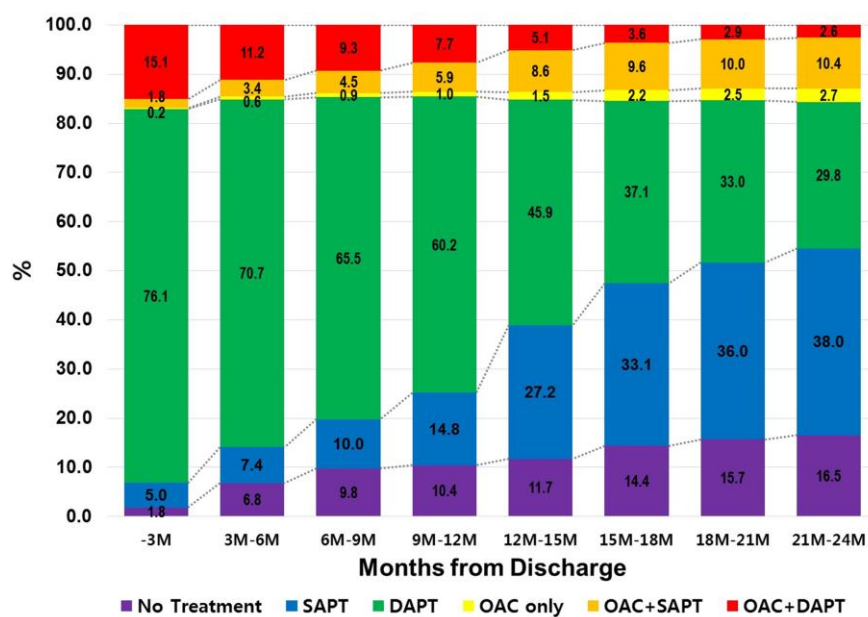
## Figure legends

### Figure 1: Prescription patterns of antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention

Most patients (76.1%) were prescribed DAPT at discharge; however, only 17.1% of the patients received OAC at discharge. During the follow-up, the proportion of patients receiving OAC remained <20% of the total population.

DAPT=dual antiplatelet therapy, OAC=oral anticoagulants, PCI=percutaneous coronary intervention, SAPT=single antiplatelet therapy

Figure 1.

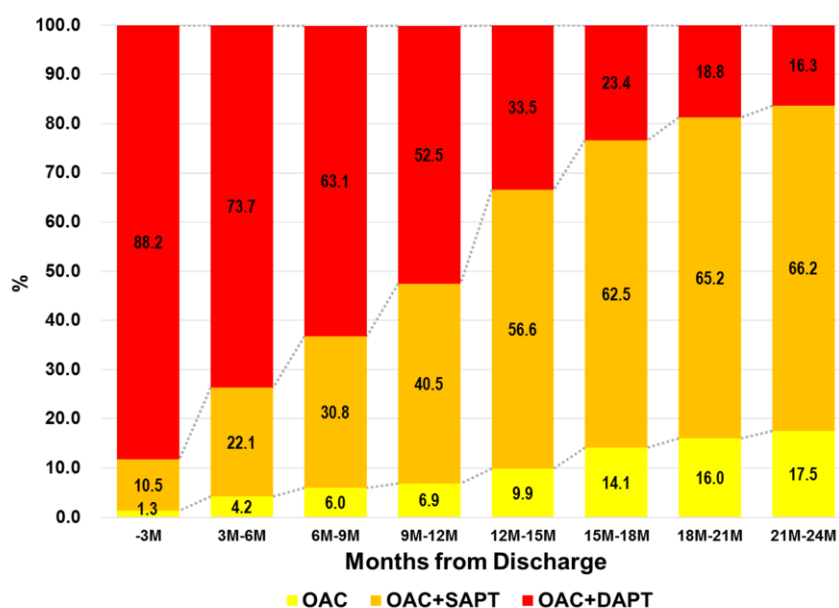


## Figure 2: Prescription patterns of oral anticoagulants in patients with atrial fibrillation undergoing percutaneous coronary intervention

Among patients receiving OAC, 88.2% received triple therapy at discharge, which gradually decreased thereafter. At the 1-year time point after PCI, 33.5% and 56.6% of the patients receiving OAC concomitantly received DAPT and SAPT respectively, whereas only 9.9% received OAC monotherapy. The OAC monotherapy prescription rate remained <20% during the follow-up.

DAPT=dual antiplatelet therapy, OAC=oral anticoagulants, PCI=percutaneous coronary intervention, SAPT=single antiplatelet therapy

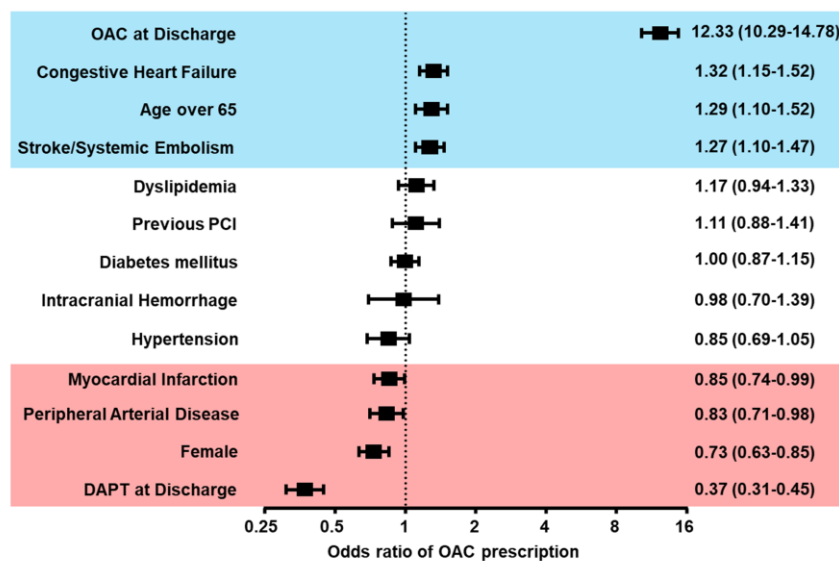
Figure 2.



### Figure 3: Factors associated with the oral anticoagulant prescription rate a year after percutaneous coronary intervention

The OAC prescription rate at discharge, a history of congestive heart failure, stroke or systemic embolism, and old age were associated with higher OAC prescription rates. A history of myocardial infarction, peripheral artery disease, female sex, and the DAPT prescription rate at discharge were related to the underutilization of OAC a year after PCI. DAPT=dual antiplatelet therapy, OAC=oral anticoagulants, PCI=percutaneous coronary intervention, SAPT=single antiplatelet therapy

Figure 3.



**Table 1. Baseline characteristics of patients based on oral anticoagulant prescriptions**

Variable	1-year after Percutaneous Coronary Intervention		P value
	No Oral Anticoagulants	Oral Anticoagulants	
	(N=7,207)	(N=1,684)	
Age (years)	68.7±9.5	69.4±8.3	0.013
Age >65 years	5,066 (70.3%)	1,275 (75.7%)	<0.001
Men	4,421 (61.3%)	1,160 (68.9%)	<0.001
Diabetes Mellitus	2,740 (38.0%)	678 (40.3%)	0.089
Hypertension*	6,332 (87.9%)	1,477 (87.7%)	0.864
Dyslipidemia <sup>†</sup>	6,000 (83.3%)	1,342 (79.7%)	<0.001
Congestive Heart Failure	2,588 (35.9%)	812 (48.2%)	<0.001
Myocardial Infarction	2,256 (31.3%)	479 (28.4%)	0.022
Previous Percutaneous Coronary Intervention	716 (9.9%)	131 (8.4%)	0.051
Peripheral Vascular Disease	1,764 (24.5%)	355 (21.1%)	0.003
Stroke or Systemic Thromboembolism	1,918 (26.6%)	675 (40.1%)	<0.001

<b>Intracranial Hemorrhage</b>	257 (3.6%)	71 (4.2%)	0.203
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc Score</b>	4.4±1.9	4.7±1.8	<0.001
0–1	352 (4.9%)	50 (3.0%)	<0.001
2 ≤	6,797 (95.0%)	1,631 (97.0%)	
<b>Oral Anticoagulants at Discharge</b>	564 (7.8%)	1,149 (68.2%)	<0.001
<b>Dual Antiplatelet Therapy at Discharge</b>	6,661 (92.4%)	721 (42.8%)	<0.001

Values are presented as numbers (percentage) unless otherwise indicated.

\*Defined as patients with diagnostic code (the International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] code) of I10-I13, I15; and minimum 1 prescription of anti-hypertensive drug (thiazide, loop diuretics, aldosterone antagonist, alpha-/beta-blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker).

†Defined as patients with diagnostic code (ICD-10-CM) of E78