Received: 31 August 2018 | Accepted: 6 March 2019

DOI: 10.1002/joa3.12183

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

Status of international normalized ratio control and treatment patterns in patients with nonvalvular atrial fibrillation taking vitamin K antagonist with or without antiplatelet therapy: Results from KORAFII registry

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Funding information
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Abstract

Background: Studies have shown that the concomitant use of a vitamin K antagonist (VKA) and an antiplatelet (APL) drug increased the bleeding risk and was less effective at preventing ischemic events. This study aimed to investigate the control status of international normalized ratio (INR) and the discontinuation rate of a VKA in patients taking VKA plus an APL drug compared with those taking a VKA alone.

Methods: Data were extracted from the KORean Atrial Fibrillation Investigation II registry, a multicenter noninterventional prospective observational study. Nonvalvular atrial fibrillation (NVAF) patients with $CHADS_2$ scores ≥ 1 who newly started (within 3 months) a VKA were enrolled and followed up for 1 year.

Results: A total of 866 NVAF patients (mean age, 67.7 years; 60.3% men) without a bleeding history were divided into the VKA+APL (n = 229) and VKA alone (n = 637) groups. During follow-up, mean INR level was lower in the VKA+APL group than in the VKA alone group (1.7 ± 0.8 vs 1.9 ± 0.9, $P = 0.0005$). INR levels were poorly controlled in both groups (66.1% and 64.7%, respectively). Patients in the VKA+APL group more frequently discontinued VKA than patients in the VKA alone group (28.8% vs 24.2%, $P = 0.045$). Major causes of VKA discontinuation were uncontrolled INR level and patient dissatisfaction or concerns.

Conclusions: The conditions of NVAF patients were inadequately controlled with VKA with or without an APL. These findings suggest that other antithrombotic treatment options are warranted in NVAF patients to achieve INR control.

KEYWORDS
anticoagulants, atrial fibrillation, International normalized ratio, platelet aggregation inhibitors, Warfarin

1 | INTRODUCTION

Atrial fibrillation (AF) carries the highest risk of stroke and thromboembolism, and its prevalence increases with increasing life expectancy.[1,2] Risk-based oral antithrombotic therapy is recommended for all patients with AF.[3] In patients with nonvalvular AF, vitamin K antagonists (VKA) have traditionally been used as oral anticoagulants (OAC) but have recently been replaced by novel oral anticoagulants (NOAC).

Approximately 56% and 11% of AF patients have concomitant cardiovascular disease including ischemic heart disease and peripheral arterial disease, respectively.[4,5] Current guidelines recommend that concomitant antiplatelet (APL) therapy and OAC therapy are indicated APL in patients with high embolic risk AF,[3] but this combination therapy is known to increase one's bleeding risk.[6,7] VKA has considerable limitations including its narrow therapeutic window and interaction with other drugs, which may increase the patient's bleeding risk. Several previous studies of the combined use of APL and VKA showed a reduced benefit for preventing thromboembolic or bleeding events compared with VKA monotherapy.[8,9] However, data are lacking about the control status of VKA in patients who are taking VKA+APL compared to VKA monotherapy.

This study aimed to investigate the appropriate use of anticoagulation with VKA by evaluating the control status of INR and the discontinuation rate of VKA in patients taking VKA+APL compared with those taking VKA alone in Korean clinical practice.

2 | METHODS

2.1 | Study design and study population

The Korean Atrial Fibrillation Investigation II was a multicenter noninterventional prospective study that enrolled 877 patients between April 2013 and March 2014 at 20 tertiary hospitals in the Republic of Korea. The patients who met all of the following criteria were included: 1) age ≥ 20 years; 2) NVAF diagnosis and a $CHADS_2$ score ≥ 1; 3) newly started VKA (within the previous 3 months) for the prevention of stroke and thromboembolism; 4) available for regular INR monitoring and follow-up of 1 year; and 5) ability to understand the study protocol and willingness to complete the subject information sheet and informed consent form. This study was approved by the Institutional Review Boards of all participating institutions. All procedures have been performed in accordance with the hospital's ethics standards and the 1964 Declaration of Helsinki. All patients provided informed consent prior to enrolling in the study.

2.2 | Data collection and follow-up

All variables were collected by medical chart reviews. All data were collected prospectively until the end of 1-year follow-up. Follow-up data after enrollment were obtained when the patients visited the hospitals regularly. Demographic features, clinical characteristics including risk factors of stroke or bleeding, and information about VKA treatments were collected at baseline. At follow-up, the VKA dose, INR levels, reasons for changing the VKA dose or changing from VKA to another drug, and concomitant APL type were investigated via medical chart reviews. In addition, whether there was a permanent discontinuation of VKA, the reasons for the discontinuation, and the type of drug changed were recorded.

2.3 | Treatment

VKA treatments including discontinuation, switching to NOAC, or adding APL were clinically decided at the physician's discretion. Adding APL indicated aspirin 100 mg and/or clopidogrel 75 mg were administered.

2.4 | End points and definition

The primary end point was the achievement of the optimal INR range evaluated by the point prevalence of patients with the optimal INR range and proportion of tests within the optimal INR range (PTR), which was defined as well-controlled for ≥ 60% during the 12 months of therapy. The secondary end point was the persistence rate of VKA treatment, and the reason for discontinuing VKA or switching to other drugs was investigated. Clinically relevant bleeding was a composite of major and minor bleeding according to Thrombolysis in Myocardial Infarction criteria and bleeding requiring medical attention.

2.5 | Statistical analysis

Comparisons of patient's characteristics between the groups were made by Student's *t* test or the Mann-Whitney U test for numerical variables or the Chi-square test for categorical variables as appropriate. In multiple response items, the Chi-square test for an equality of proportions was used to identify the differences between the two groups.

During the follow-up from the baseline, INR values were collected to investigate the quality of VKA. The achievement of optimal INR range (INR 2.0–3.0) in patients prescribed VKA only or VKA+APL was evaluated by point prevalence of patients with optimal INR range and PTR, which was defined as well-controlled for ≥ 60%.

For bleeding events and discontinuation events of VKA use, 1-year event rates were calculated using Kaplan–Meier analysis. Among the two groups, differences in the event rates were analyzed using the log-rank test.

All statistical analyses were conducted with SAS software version 9.4 (SAS Institute, Cary, NC, USA), and a two-tailed *P* value < 0.05 was considered statistically significant.

TABLE 1 Baseline features of the patients without a bleeding history

	Total (N = 866)	VKA with APL (N = 229)	VKA without APL (N = 637)	*P*-value
Male, n (%)	522 (60.3)	133 (58.1)	389 (61.1)	0.43[a]
Age, y	67.7 ± 10.1	67.1 ± 10.1	67.9 ± 10.1	0.32[b]
<65, n (%)	308 (25.6)	86 (37.6)	222 (34.9)	0.66[a]
65-74, n (%)	286 (33.0)	81 (35.4)	205 (32.2)	
≥75, n (%)	272 (31.4)	62 (27.1)	210 (33.0)	
BMI (kg/m^2)	24.8 ± 3.2	25.2 ± 3.3	24.7 ± 3.2	0.07[b]
AF duration (mo)	18.2 ± 34.0	22.3 ± 33.9	16.7 ± 34.0	0.014[c]
Type of AF, n (%)				<0.0001[a]
First diagnosed	93 (10.7)	29 (12.7)	64 (10.1)	
Paroxysmal	267 (30.8)	70 (30.6)	197 (30.9)	
Persistent	343 (39.6)	66 (28.8)	277 (43.5)	
Long-standing persistent	42 (4.9)	23 (10.0)	19 (3.0)	
Permanent	82 (9.5)	27 (11.8)	55 (8.6)	
Unknown	39 (4.5)	14 (6.1)	25 (3.9)	

Abbreviations: AF, atrial fibrillation; APL, antiplatelet; BMI, body mass index; VKA, vitamin K antagonists.

[a]*P* value calculated by the chi-squared test.

[b]*P* value calculated by Student's *t* test.

[c]*P* value calculated by the Mann-Whitney *U* test.

TABLE 2 Thromboembolic and bleeding risks of the study population

	Total (N = 866)	VKA with APL (N = 229)	VKA without APL (N = 637)	*P*-value
CHA_2DS_2-VASc score	3.0 ± 1.4	3.04 ± 1.5	2.91 ± 1.34	0.22[a]
1	136 (15.7)	42 (18.3)	94 (14.8)	
2	218 (25.2)	42 (18.3)	176 (27.6)	
3	226 (26.1)	58 (25.3)	168 (26.4)	
4	170 (19.6)	53 (23.1)	117 (18.4)	
5	79 (9.1)	22 (9.6)	57 (9.0)	
6	33 (3.8)	10 (4.4)	23 (3.6)	
7	2 (0.2)	1 (0.4)	1 (0.2)	
8	2 (0.2)	1 (0.4)	1 (0.2)	
Factors of CHA_2DS_2-VASc score				
History of CHF	151 (17.4)	44 (19.2)	107 (16.8)	0.41[b]
Hypertension	677 (78.2)	175 (76.4)	502 (78.8)	0.45[b]
Age 65-74	286 (33.0)	81 (35.4)	205 (32.2)	0.38[b]
Age ≥ 75	272 (31.4)	62 (27.1)	210 (33.0)	0.10[b]
Diabetes	227 (26.2)	61 (26.6)	166 (26.1)	0.86[b]
Stroke	142 (16.4)	50 (21.8)	92 (14.4)	0.010[b]
Vascular disease	40 (4.6)	16 (7.0)	24 (3.8)	0.047[b]
Female	344 (39.7)	96 (41.9)	248 (38.9)	0.43[b]
HAS-BLED score	1.5 ± 0.6	1.9 ± 0.7	1.2 ± 0.5	<0.0001[a]
1	434 (61.4)	64 (28.0)	370 (77.4)	
2	224 (31.7)	123 (53.7)	101 (21.1)	
3	47 (6.7)	41 (17.9)	6 (1.3)	
4	2 (0.3)	1 (0.4)	1 (0.2)	
Factors of HAS-BLED score[c]				
Hypertension	32 (3.7)	7 (3.1)	25 (3.9)	0.55[b]
Abnormal renal	13 (1.5)	2 (0.9)	11 (1.7)	0.36[b]
Abnormal liver	1 (0.1)	1 (0.4)	0 (0.0)	0.095[b]
Stroke	107 (12.4)	33 (14.4)	74 (11.6)	0.27[b]
Bleeding	0 (0.00)	0 (0.0)	0 (0.0)	—
Labile INRs	72 (8.3)	12 (5.2)	60 (9.4)	0.050[b]
Elderly (Age > 65)	529 (61.1)	135 (59.0)	394 (61.9)	0.44[b]
Drug/Alcohol				
Antiplatelet	229 (26.4)	229 (100.0)	0 (0.0)	<0.0001[b]
Aspirin	191 (83.4)	191 (83.4)	0 (0.0)	
Clopidogrel	17 (7.4)	17 (7.4)	0 (0.0)	
DAPT	18 (7.9)	18 (7.9)	0 (0.0)	
Other	3 (1.3)	3 (1.3)	0 (0.0)	
NSAIDs	0 (0.00)	0 (0.0)	0 (0.0)	—
Alcohol history	48 (5.5)	18 (7.9)	30 (4.7)	0.074[b]

Abbreviations: DAPT, dual anti platelet therapy; INR, international normalized ratio; NSAIDs, non-steroidal anti-inflammatory drugs.

[a]*P* value calculated by the Mann-Whitney *U* test.

[b]*P* value calculated by the chi-squared test for equal proportions between groups.

[c]Multiple response items.

TABLE 3 INR control status

	Total (N = 866)	VKA with APL (N = 229)	VKA without APL (N = 637)	*P*-value
VKA dosage (mg/d), mean ± SD (N)	2.7 ± 1.3 (865)	2.6 ± 1.1 (229)	2.7 ± 1.3 (363)	0.07[a]
Mean INR level[b] (mg/d), mean ± SD (N)	1.9 ± 0.9 (520)	1.7 ± 0.8 (86)	1.9 ± 0.9 (434)	0.0005[c]
INR level[b], N (%)		86 (100)	434 (100)	0.016[a]
<2	339 (65.2)	67 (77.9)	272 (62.7)	
2-3	132 (25.4)	16 (18.6)	116 (26.7)	
>3	49 (9.4)	3 (3.5)	46 (10.6)	
PTR[d] ≥60%, N (%)	251 (34.9)	62 (33.9)	189 (35.3)	0.74[a]

Abbreviations: APL, antiplatelet; INR, international normalized ratio; PTR, proportion of tests within optimal INR range; VKA, vitamin K antagonists.
[a]*P* value calculated by the chi-squared test.
[b]Results in old patient group at baseline.
[c]*P* value calculated by the Mann-Whitney *U* test.
[d]Results in patients for whom follow-up data were available.

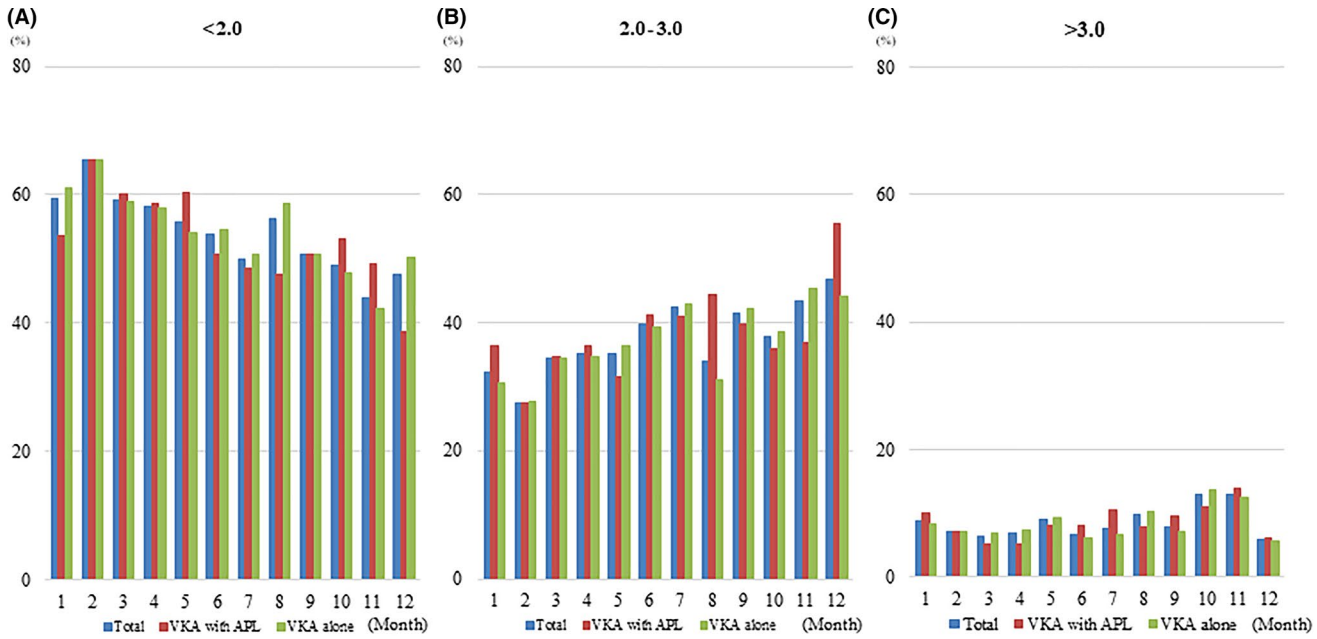


FIGURE 1 Trend of INR control status of patients with or without APL use during the 12-month follow-up. (A) Proportion of patients with an INR<2. (B) Proportion of patients with an INR of 2-3. (C) Proportion of patients with an INR>3. VKA, vitamin K antagonists; APL, antiplatelet; INR, international normalized ratio

3 | RESULTS

3.1 | Patients

Among the 877 NVAF patients in the KORean Atrial Fibrillation Investigation (KORAF) II registry, 866 (98.7%) without a bleeding history were analyzed. The mean patient age was 67.7 ± 10.1 years; 60.3% of them were male. Patients were divided into the VKA+APL group (n = 229) and the VKA alone group (n = 637). The patients' baseline characteristics are summarized in Table 1. There was no intergroup difference in age or sex. The proportion of patients with paroxysmal AF was similar between groups; however, there was a higher proportion of patients with nonparoxysmal AF in the VKA alone group than in the VKA+APL group. However, AF duration was longer in the VKA+APL group than in the VKA alone group (22.3 ± 33.9 vs 16.7 ± 34.0, respectively, *P* = 0.01).

3.2 | Thromboembolic risk and bleeding risk

The factors contributing to the CHA_2DS_2-VASc and HAS-BLED scores are shown in Table 2. There was no intergroup difference

TABLE 4 VKA discontinuation and switching type

	Total (N = 866)	VKA with APL (N = 229)	VKA without APL (N = 637)	*P*-value[a]
Discontinue VKA	214 (25.4)	64 (28.8)	150 (24.2)	0.29
Switch to NOAC	57	15	42	
Switch to Aspirin	58	19	39	
Switch to clopidogrel	21	4	17	
Switch to DAPT	15	5	10	
Switch to others	4	1	3	
No switch	59	20	39	

Abbreviations: APL, antiplatelet; DAPT, dual anti platelet therapy; NOAC, novel oral anticoagulant; VKA, vitamin K antagonists.
[a]*P* value calculated by the chi-squared test.

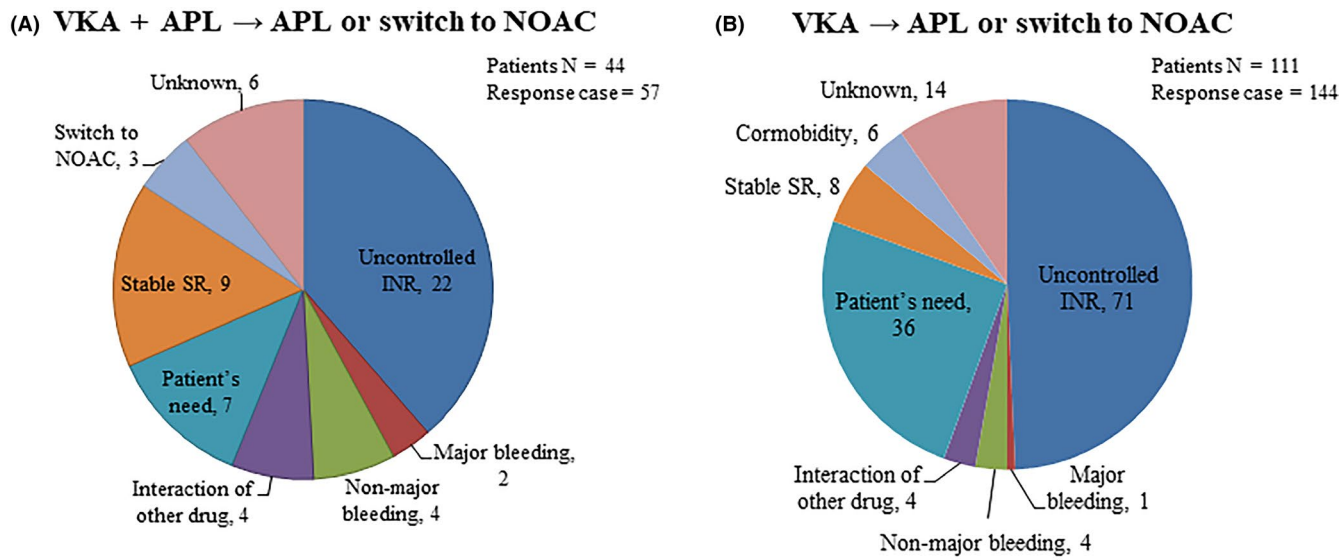


FIGURE 2 Major cause of VKA discontinuation: (A) In patients treated with VKA and APL combination therapy; and (B) In patients treated with VKA alone therapy. VKA, vitamin K antagonist; APL, antiplatelet; Multiple responses were allowed; Unit was presented as response cases

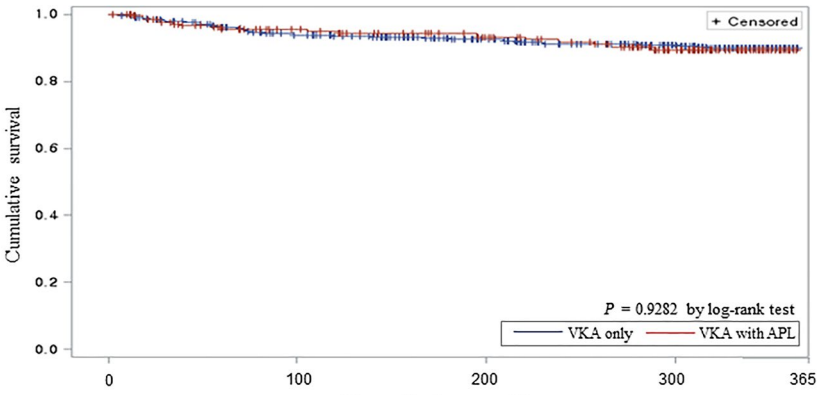
in CHA_2DS_2-VASc score (3.0 ± 1.5 and 2.9 ± 1.3, $P = 0.22$ for the VKA+APL and VKA alone groups, respectively), while the distribution of factors was similar between the two groups except for stroke and vascular disease. More patients had a history of previous stroke and vascular disease in the VKA+APL group than in the VKA alone group (21.8% vs 14.4%, respectively, $P = 0.01$; 7.0% vs 3.8%, respectively, $P = 0.047$). The HAS-BLED score was slightly higher in the VKA+APL group than in the VKA alone group (1.9 ± 0.7 vs 1.3 ± 0.5, respectively, $P < 0.001$). All patients in the VKA+APL group were taking at least 1 APL, while 18 patients (7.9%) were on dual APL therapy (DAPT).

3.3 | INR control

During follow-up, the mean INR level was lower in the VKA+APL group than in the VKA alone group (1.66 ± 0.8 vs 1.94 ± 0.94, respectively, $P = 0.0005$); however, there was no intergroup difference in a PTR of 60% (33.9% vs 35.3%, respectively, $P = 0.74$) (Table 3). Among all patients who took VKA long term, the number with a suboptimal INR level (INR < 2) decreased and the number within the optimal INR range increased. However, for 12 months of follow-up, >50% of patients were out of the optimal INR level range; the VKA alone and VKA+APL groups showed similar trends (Figure 1).

3.4 | Discontinuation of VKA

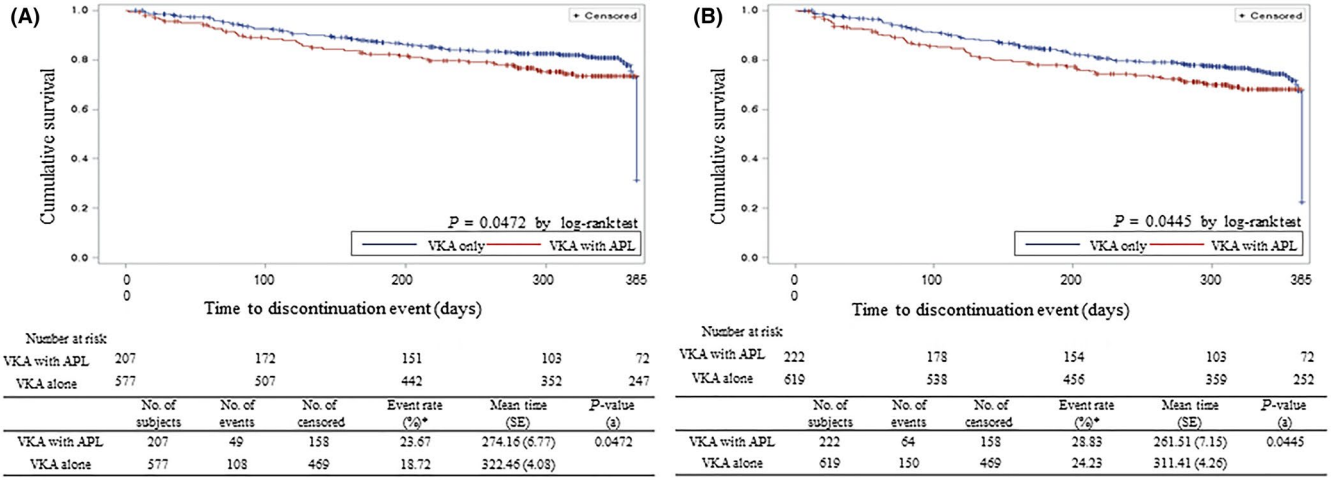
Sixty-four (28.8%) patients in the VKA+APL group and 150 (24.2%) in the VKA alone group discontinued VKA. Fifteen (6.6%) patients in the VKA+APL group and 42 (6.6%) patients in the VKA alone group switched all medications to NOAC. A total of 29 (12.7%) patients in the VKA+APL group discontinued VKA and remained on APL only, while 69 (10.8%) patients in the VKA alone group started an APL agent other than VKA (Table 4). The most common reason for starting NOAC instead of the previous medication was uncontrolled INR level.



Number at risk					
VKA with APL	222	171	142	93	72
VKA alone	619	502	419	324	251

	No. of subjects	No. of events	Event rate (%)*	Mean time (SE)	*P*-value (a)
VKA with APL	222	18	8.11	272.38 (4.11)	0.9282
VKA alone	619	52	8.40	296.95 (2.85)	

FIGURE 3 One-year cumulative incidence of bleeding events during the follow-up. VKA, vitamin K antagonist; APL, antiplatelet; CI, confidence interval; SE, standard error. *By Kaplan-Meier analysis; (a) log-rank test analysis



Number at risk					
VKA with APL	207	172	151	103	72
VKA alone	577	507	442	352	247

	No. of subjects	No. of events	No. of censored	Event rate (%)*	Mean time (SE)	*P*-value (a)
VKA with APL	207	49	158	23.67	274.16 (6.77)	0.0472
VKA alone	577	108	469	18.72	322.46 (4.08)	

Number at risk					
VKA with APL	222	178	154	103	72
VKA alone	619	538	456	359	252

	No. of subjects	No. of events	No. of censored	Event rate (%)*	Mean time (SE)	*P*-value (a)
VKA with APL	222	64	158	28.83	261.51 (7.15)	0.0445
VKA alone	619	150	469	24.23	311.41 (4.26)	

FIGURE 4 Discontinuation rate of VKA therapy: (A) In patients excluding those who changed the therapy from VKA to NOAC; and (B) In patients including those who changed the therapy from VKA to NOAC. VKA, vitamin K antagonists; NOAC, novel oral anticoagulant; APL, antiplatelet; CI, confidence interval; SE, standard error. *By Kaplan-Meier analysis; (a) log-rank test analysis

The major causes of VKA discontinuation were uncontrolled INR level, major bleeding, and clinically relevant nonmajor bleeding. (Figure 2). There was no intergroup difference in clinically relevant bleeding events (Figure 3). Among all patients except those who changed the therapy from VKA to NOAC during follow-up, those in the VKA+APL group more frequently discontinued VKA therapy than those in the VKA alone group (23.7% vs 18.7%, respectively, $P = 0.047$) (Figure 4A). Including the patients who changed the therapy from VKA to NOAC, more patients discontinued VKA in VKA+APL group than in the VKA alone group (28.8% vs 24.2%, respectively, $P = 0.045$) (Figure 4B).

4 | DISCUSSION

The major findings of this study were that a lower proportion of individuals taking VKA achieved the optimal INR level with or without additional APL and that patients taking VKA+APL showed lower mean INR values than those taking VKA alone. More patients in the VKA+APL group discontinued VKA during the 1-year follow-up than in the VKA alone group. The main reasons for this were not only bleeding events but also physician concern about bleeding caused by unstable INR levels and interaction with other medications. Among the patients who discontinued the VKA, more than half of physicians in both groups abandoned the OAC therapy rather than switching to NOAC.

APL drugs prevent vascular endothelial hemostasis by dysregulating platelet aggregation, while VKA prevent thrombosis by inhibiting clotting protein formation. The different main targets of these drugs demonstrated that each medication is superior to the other in certain medical conditions: APL therapy reduces the frequency of ischemic events after percutaneous coronary intervention (PCI), while OAC therapy significantly reduces the incidence of

thromboembolism compared with APL therapy in AF patients.[10] The current guidelines recommend OAC and APL combination therapy who are indicated APL therapy in individuals taking OAC due to the high embolic risk related to AF[3]; however, because of the increased risk of bleeding with combination therapy, the efficacy of minimal use of APL in NVAF patients has been studied. In the general population, maintaining DAPT for a long-term duration decreased stent thrombosis and major adverse cardiovascular and cerebrovascular events in patients treated with drug-eluting stents (DES)[11]; however, the WOEST study showed that in patients taking OAC, single APL therapy had similar efficacy to and decreased bleeding events compared to DAPT.[6] In cases of stable coronary artery disease, VKA+APL combination therapy increased risk of bleeding than VKA monotherapy without reduction in risk of recurrent coronary events or thromboembolism.[7]

However, previous studies in practice showed that VKA+APL combination therapy did not reduce the risk of stroke more than VKA monotherapy. Without a history of coronary intervention, a Danish national cohort showed that VKA monotherapy was better able to prevent primary MI and stroke than aspirin (ASA) alone or VKA+ASA combination therapy; importantly, combination therapy was not associated with better prevention, and the bleeding risk increased.[8] In a large Japanese cohort undergoing PCI, 8.3% of patients were diagnosed with AF, OAC therapy was underused, and its intensity was mostly suboptimal in patients maintaining DAPT; subsequently, OAC therapy was not associated with improved stroke prevention compared to no OAC therapy.[9] A Korean single-center study demonstrated similar results among patients receiving DES implantation: 7.1% patients had a diagnosis of AF at the index PCI, only approximately 10% were treated with OAC+DAPT, and treatment was not associated with decreased ischemic events but was associated with increased bleeding risk compared to DAPT alone.[12] There was a lack of information about INR value or control status of OAC in previous studies; in our analysis, a higher rate of discontinuation and suboptimal treatment of VKA in the VKA+APL group support the less favorable results of VKA+APL combination therapy than VKA monotherapy for preventing stroke events. Bleeding events and concerns caused by VKA instability made more physicians underuse or discontinue OAC therapy in the VKA+APL group than in the VKA alone group, a practice that can lead to inadequate stroke prevention in AF patients.

In the era of NOAC, a large randomized trial was performed to identify the optimal treatment strategy for patients who required simultaneous APL and OAC therapy. The PIONEER AF-PCI trial provided evidence that, in the acute stage of undergoing PCI, dose-adjusted factor Xa inhibitor+APL was associated with a lower bleeding rate and similar efficacy outcomes compared with VKA+APL in NVAF patients, but the efficacy benefit was uncertain.[13] Clinical trials with another factor Xa inhibitor (apixaban and edoxaban) and direct thrombin inhibitor (dabigatran) to determine the safety and efficacy of NOAC in patients undergoing PCI are ongoing; these trials will provide further evidence of the role of NOAC for patients who require simultaneous OAC and APL use.

A previous retrospective study of a Korean cohort showed that only 42.4% of patients achieved an optimal INR level[14]; in other words, more than half of the patients on VKA therapy are exposed to the potential risk of thromboembolic events. This prospective study showed similar results; specifically, no difference was seen in PTR ≥ 60% in the simultaneous VKA+APL use versus VKA alone groups. These results suggest that administration of APL does not effect to PTR status compared with no administration of APL; VKA therapy itself has a limitation in maintaining optimal OAC due to unstable PTR. NOAC is expected to improve the ability of OAC therapy to prevent thromboembolism by improving patient compliance and minimizing fluctuations in VKA concentrations. However, underuse of NOAC is another concern. In the real-world data of NOAC therapy, approximately 15% of patients were treated with a reduced dose despite having sufficient renal function.[15] For optimal results to prevent thromboembolic events with OAC therapy, attention needs to be paid to avoid under-dosing in the absence of an obvious reason.

4.1 | Study limitations

This study has several limitations. First, the relationship between INR level and rates of major adverse cardiac events was not studied. Second, indication of APL in VKA+APL group patients was not collected that baseline characteristics showed only factors of CHA_2DS_2-VASc score that do not include history of coronary artery disease except MI or type of stroke. Although the OAC and APL combination therapy increased the bleeding risk, it should have been prescribed to obviously indicated patients. Third, this study was a prospective observational study comparing between VKA+APL group and VKA only users, the underlying medical condition might be different. The confounding from differences in the demographic and clinical characteristics may exist.

5 | CONCLUSIONS

The conditions of more than half of the patients treated with VKA in this cohort were under-controlled regardless of APL use or non-use. Patients in the VKA+APL group showed a lower mean INR level and a higher VKA discontinuation rate than those in the VKA alone group. Physicians discontinued the OAC therapy due to their concern about unstable INR levels or interactions with other medications. These findings suggest that other antithrombotic treatment options (i.e. NOAC or non-pharmacologic therapy) are warranted in NVAF patients. Further investigations of a standardized strategy for managing this double-edged treatment are needed for the optimal prevention of ischemic stroke and bleeding events in NVAF patients.

ACKNOWLEDGEMENTS

This research was sponsored by BMS/Pfizer Pharmaceuticals Korea Ltd. All authors have no other conflict of interest.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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How to cite this article: Park H-S, Kim Y-H, Kim JS, et al. Status of international normalized ratio control and treatment patterns in patients with nonvalvular atrial fibrillation taking vitamin K antagonist with or without antiplatelet therapy: Results from KORAFII registry. *J Arrhythmia*. 2019;35:593–601. https://doi.org/10.1002/joa3.12183