

Original Research

Bleeding risk in patients with atrial fibrillation treated with combined anti-platelet and non-vitamin K antagonist oral anticoagulant therapyDong Geum Shin¹, Sunhwa Kim², Yoo Ri Kim^{3,*}¹Division of Cardiology, Department of Internal medicine, Hallym University Kangnam Sacred Heart Hospital, 07226 Seoul, Republic of Korea²Division of Cardiology, The Catholic University of Korea, Incheon St. Mary's Hospital, 21431 Incheon, Republic of Korea³Division of Cardiology, Department of Internal medicine, Dongguk University College of Medicine, Ilsan Hospital, Goyang-si, 10326 Gyeonggi-do, Republic of Korea*Correspondence: yul@dumc.or.kr (Yoo Ri Kim)

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Abstract

Background: The use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with non-valvular atrial fibrillation (AF) has been increasing. Accordingly, the combined use of antiplatelet agents (APT) and NOAC therapy is commonly encountered in clinical practice. The purpose of this study was to compare the clinical outcomes between combination therapy (NOAC and APT) vs. monotherapy (NOAC only) in patients with AF. **Methods:** We retrospectively analyzed patients who were prescribed NOACs between January 2012 and December 2016. The primary outcome was major bleeding and any bleeding events, and the secondary outcomes were stroke/systemic embolic (SE) events and major adverse cardiac events (MACE). **Results:** Of the 1068 participants, there were 264 (24.7%) patients in the combination therapy group. The prevalence of diabetes ($p = 0.017$) and history of stroke and transient ischemic attacks ($p < 0.001$) was higher in the combination group than in the monotherapy group. During the mean 14.6 ± 9.8 months of follow-up, the incidence of any bleeding was significantly higher in the combination therapy group than in the monotherapy group ($p < 0.001$). The rate of major bleeding, stroke/SE, and MACE between the two groups was similar. The rate of under-dosage NOAC prescriptions was higher in the combination therapy group than in the monotherapy group ($p = 0.024$). **Conclusions:** The combination therapy group had higher incidences of any bleeding events compared to the monotherapy in patients with appropriate dosing. However, there was no difference in stroke/SE, and MACE. The bleeding risk in AF patients taking the combination of NOACs and APT should be carefully evaluated.

Keywords: Antiplatelet agents; Atrial fibrillation; Bleeding; Non-vitamin K oral anticoagulant**1. Introduction**

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia. According to the guidelines, it is estimated that 15% of strokes occur in patients with AF [1]. Thus, oral anticoagulants (OACs) have been the cornerstone of stroke and systemic embolism (SE) prophylaxis in patients with AF. Several studies including both randomized controlled trials and real world-settings have shown that non-vitamin K antagonist oral anticoagulants (NOACs) in patients with non-valvular AF were more effective than warfarin in preventing thromboembolic events and reducing the risk of bleeding events [2–6]. Therefore, NOACs are preferred over warfarin, and NOAC prescriptions have increased rapidly [7].

Most patients with AF also have various risk factors for atherosclerotic cardiovascular diseases [8]. Therefore, the proper strategy of combination of OACs and antiplatelet therapy (APT) in many conditions has great clinical impact. However, current strategies combining OACs and APT therapies have led to a significant increase in bleeding rates [9,10]. Studies have reported conflicting results regarding the combination of OACs and APT to optimize

ischemia and bleeding risk. For this reason, finding the optimal balance of the appropriate treatments for each patient with indicators for both treatments is critical in achieving clinical benefits.

Compared to prescribing adequate warfarin doses according to the prothrombin time, each NOAC has a recommended dose based on the clinical characteristics of the patient, and criteria are provided for dose reduction. Although NOAC prescriptions have increased gradually, the number of patients receiving an under-dosing NOACs for various reasons has also increased [11,12]. However, patients with AF who are receiving suboptimal medical therapy are at an increased risk of stroke, cardiovascular hospitalization, and mortality [13].

The main objective of this retrospective study was to evaluate the clinical safety and efficacy of combination therapy (NOAC and APT) compared to monotherapy (NOAC only) in a real-world cohort of AF patients. In addition, we aimed to investigate whether the under-dosing of NOACs was effective or safe.



2. Methods

2.1 Study population

We retrospectively analyzed 1068 consecutive patients who were prescribed initiating NOACs for AF at Catholic University St. Mary's Hospital, in Incheon, Korea between January 2012 and December 2016. The diagnosis of AF was based on a 12-lead electrocardiogram characterized by the absence of discrete P-waves and an irregular ventricular rate. Paroxysmal AF (PAF) was defined in patients with a history of ≥ 1 episode of self-terminating AF that lasted ≤ 7 days. The inclusion criteria were non-valvular AF patients who were taking NOACs and some of them were taking APT. The exclusion criteria were patients less than 18 years old, with a history of NOAC therapy, mechanical prosthetic valves or moderate-to-severe mitral stenosis, and impaired renal function [creatinine clearance (CrCl) < 30 mL/min and dialysis]. We also excluded patients with coronary or peripheral artery disease undergoing stent implantation within the last 12 months. The patients were divided into combination therapy or monotherapy groups according to whether or not APT was administered with NOACs. All case records were reviewed following a standardized data collection protocol for the purpose of obtaining information. The authors had full access to and take full responsibility for the integrity of the data. The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board.

2.2 Antiplatelet agents and NOACs

The types and doses of APT administered included aspirin, triflusal, P2Y₁₂ inhibitors, or cilostazol taken for various reasons or no apparent reason. There were three types of NOACs administered, apixaban, dabigatran, and rivaroxaban. A standard dose was defined as apixaban at 5 mg twice daily, dabigatran at 150 mg twice daily, and rivaroxaban at 20 mg once daily. A dose reduction protocol was based on the 2018 European Heart Rhythm Association practical guideline [14]. Dabigatran was administered at 110 mg twice a day to patients with moderate renal impairment (CrCl 15–29 mL/min), those who had been taking APT or non-steroidal anti-inflammatory drugs, or patients 75 years of age or older. If in patients over 75-year-old or a CrCl was 30–50 mL/min, 15 mg of rivaroxaban was given once a day. Apixaban was administered at 2.5mg twice a day for two or more of the following three conditions: patients over 80 years old, a weight of less than 60 kg, and a serum Cr value of less than 1.5 mg/dL. When the dose was prescribed according to the above criteria, it was defined as appropriate dosing. The dosage of APT given with NOACs was prescribed according to the physician's judgment.

2.3 Clinical outcomes

The primary outcome was major bleeding and any bleeding. Major bleeding was defined as clinically overt

bleeding requiring hospital admission including a blood transfusion, decreased hemoglobin levels of ≥ 2.0 g/dL, or symptomatic bleeding in a critical area or organ. The secondary outcomes were stroke or SE, and major adverse cardiac events (MACE). Definite stroke or SE was diagnosed by the combination of both the clinical situation and radiologic studies. MACE was a composite of bleeding events, thromboembolic events, and deaths including cardiovascular, non-cardiovascular, and undetermined deaths.

2.4 Statistical analysis

The continuous variables are presented as means and standard deviations. Comparison of the continuous variables was performed using an independent *t*-test or, in case of a non-normal distribution, the Mann-Whitney test. The categorical variables are reported as counts and proportions and analyzed using Pearson's Chi-squared tests or Fisher's exact test, as appropriate. Kaplan-Meier analysis with the log-rank test was used to compare the clinical outcomes. Multivariate Cox proportional regression analysis was used to investigate any independent predictors of clinical outcomes. The SPSS statistical package (SSPS Inc., Chicago, IL, USA) was used to perform all statistical evaluations. A *p*-value of < 0.05 was considered statistically significant.

3. Results

3.1 Baseline characteristics

The study population consisted of 1068 patients with AF taking NOACs. Of these, 804 patients (75.3%) were taking monotherapy, and 264 (24.7%) were taking combination therapy. Table 1 shows a summary of the baseline characteristics of the overall study population according to the use of APT. The mean patient age was 70.5 ± 12.1 years, and 528 (49.4%) were male. The mean CHA₂DS₂-VASc score was 3.1 ± 1.6 , and 538 (50.4%) patients had PAF.

Compared to the monotherapy group, the prevalence of diabetes (25.4% vs. 18.6%, $p = 0.017$), stroke/TIA history (44.7% vs. 22.9%, $p < 0.001$) and peripheral vascular disease (0.4% vs. 2.3%, $p = 0.009$) were significantly higher in the combination therapy group. Other clinical characteristics including heart failure, hypertension, myocardial infarction and CHA₂DS₂-VASc scores demonstrated no significant difference between the groups.

3.2 Clinical outcomes

During 14.6 ± 9.8 months of follow-up, 37 (3.5%) patients had major bleeding, 86 (8.1%) patients had any bleeding, 47 (4.4%) patients had stroke or SE, and 45 (4.2%) patients died from cardiac or non-cardiac causes. The patients taking combination therapy had a higher rate of any bleeding (15.2% vs. 5.7%; $p < 0.001$) and similar rates of major bleeding, stroke or SE, and MACE (all $p > 0.05$). The types of thromboembolic and bleeding events reported in the two groups are listed in Table 2.

Table 1. Baseline characteristics of patients taking monotherapy or combination therapy.

	Overall (n = 1068)	Monotherapy (n = 804)	Combination therapy (n = 264)	p-value
Age	70.5 ± 12.1	70.4 ± 12.5	70.6 ± 11.0	0.804
Sex, male, %	528 (49.4)	384 (47.6)	145 (54.9)	0.040
Body mass index, kg/m ²	24.5 ± 3.9	24.4 ± 4.0	24.8 ± 3.8	0.208
Creatinine Clearance, mL/min	62.9 ± 27.7	62.7 ± 28.0	63.4 ± 26.7	0.454
Paroxysmal AF, %	538 (50.4)	393 (48.9)	145 (54.9)	0.088
Previous warfarin use	49 (4.6)	32 (4.0)	17 (6.4)	0.098
Medical history, %				
Heart failure	135 (12.6)	99 (12.3)	36 (12.3)	0.575
Hypertension	482 (45.3)	361 (45.1)	121 (45.8)	0.829
Diabetes mellitus	216 (20.2)	149 (18.6)	67 (25.4)	0.017
Stroke/TIA	302 (28.3)	184 (22.9)	118 (44.7)	<0.001
Myocardial infarction	29 (2.7)	21 (2.6)	8 (3.0)	0.717
Peripheral vascular disease	9 (3.6)	3 (0.4)	6 (2.3)	0.009
CHA ₂ DS ₂ -VASc score	3.1 ± 1.6	2.9 ± 1.6	3.4 ± 1.7	0.493
Echocardiographic value				
LV ejection fraction, %	58.1 ± 10.1	58.1 ± 10.2	27.9 ± 9.5	0.789
LA size (AP diameter), mm	43.8 ± 7.7	43.5 ± 7.6	44.5 ± 7.8	0.065

AF, atrial fibrillation; BMI, body mass index; CHA₂DS₂-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes mellitus, and prior ischemic Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female); LA, left atrium; TIA, transient ischemic attack.

As shown in Fig. 1, the Kaplan-Meier analysis showed a significant difference in event-free survival from any bleeding (log-rank $p = 0.018$). However, the incidence of major bleeding (log-rank $p = 0.149$), stroke or SE (log-rank $p = 0.885$), and MACE (log-rank $p = 0.916$) was not different between the two groups. As shown in the **Supplementary Tables**, Combination therapy was associated with major bleeding on multivariate Cox proportional hazard analysis (Hazard ratio [HR], 2.74; 95% confidence interval [CI]: 1.01–7.44). And old age was independent risk factor of MACE.

3.3 Preferred dose of NOAC

Table 3 shows a comparison according to the dose of NOAC. Among the entire study population, the number of patients receiving appropriate dosing was 540 (50.6%). There were 482 (45.1%) under-dosed patients, and 45 (4.2%) received over-dosages. Treatment preference was found to depend upon concomitant APT. The combination group had a lower proportion of appropriate dosage prescriptions and a higher proportion of under-dosage prescriptions than the monotherapy group.

The proportions of appropriate, under-dosage, and over-dosage prescriptions differed among NOACs. Most patients taking dabigatran and apixaban received appropriate dosage prescriptions, whereas rivaroxaban showed a higher proportion of under-dosage prescriptions. In the case

of rivaroxaban, under-dosage prescriptions were administered more in the combination group.

3.4 Clinical outcomes according to the dose of NOAC

In sub-analysis based on appropriately prescribed doses of NOACs, depending upon whether APT was taken or not, all outcomes were similar to those seen in the overall population (major bleeding: log-rank $p = 0.722$, any bleeding: log-rank $p = 0.001$, stroke or SE: log-rank $p = 0.744$, and MACE: log-rank $p = 0.237$; Fig. 2).

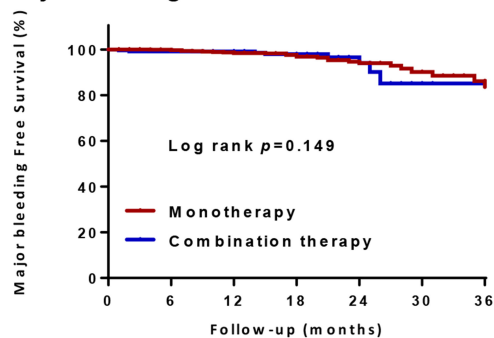
The clinical outcomes of patients prescribed appropriate monotherapy doses and under-dosages in the combination group were compared. In the Kaplan-Meier analysis, under-dosing in the combination group showed no significant difference in the event-free survival of patients with major bleeding (log-rank $p = 0.874$), any bleeding (log-rank $p = 0.810$), and MACE (log-rank $p = 0.864$) but increased stroke and SE rates (log-rank $p = 0.001$) compared to patients in the appropriate dosage monotherapy group (Fig. 3).

4. Discussion

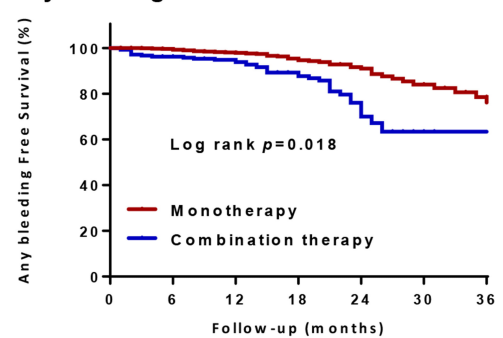
The major findings of this real-world retrospective study were that combination therapy with NOACs plus APT was (1) not uncommon, (2) increased any bleeding events but did not decrease stroke/SE events, and (3) under-dosage prescriptions of NOAC occurred at a high rate.

Table 2. Reported thromboembolic and bleeding events.

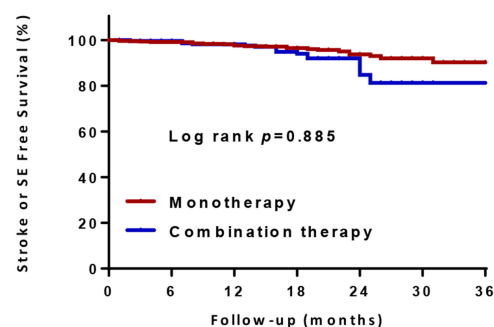
	Overall (n = 1068)	Monotherapy (n = 804)	Combination therapy (n = 264)	p-value
Thromboembolic event (%)	47 (4.4)	31 (3.9)	16 (6.1)	0.130
Stroke	44	28	16	
Systemic embolism	3	3	0	
Any bleeding event (%)	86 (8.1)	46 (5.7)	40 (15.2)	<0.001
Major bleeding (%)	37 (3.5)	29 (3.6)	8 (3.0)	0.657
Gastro-intestinal	23	19	4	
Intracranial	7	4	3	
Hemoptysis	5	4	1	
Pericardial effusion	1	1	0	
Aortic rupture	1	1	0	
Non-Major bleeding (%)	49 (4.6)	17 (2.1)	32 (12.1)	<0.001
Cutaneous	22	8	14	
Epistaxis	12	4	8	
Hematuria	9	3	6	
Oral cavity	6	2	4	

A. Major bleeding

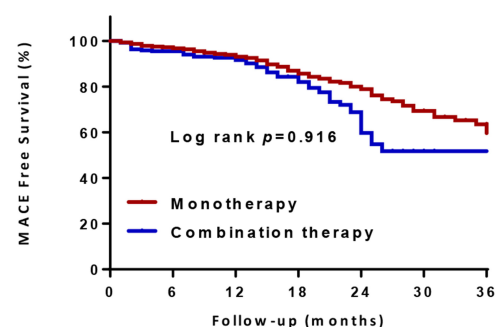
Number at Risk (months)	0	6	12	18	24
Monotherapy	803	587	481	271	110
Combination therapy	263	247	197	110	62

B. Any bleeding

Number at Risk (months)	0	6	12	18	24
Monotherapy	803	587	480	270	109
Combination therapy	263	246	196	108	60

C. Stroke or SE

Number at Risk (months)	0	6	12	18	24
Monotherapy	803	587	480	269	111
Combination therapy	263	247	184	110	61

D. MACE

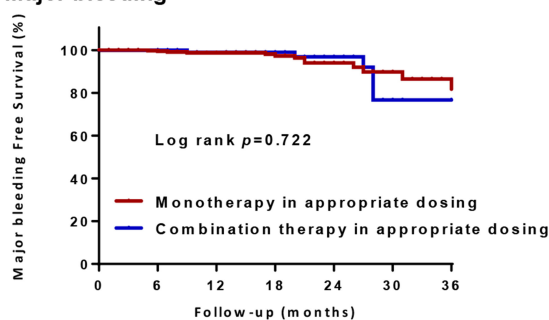
Number at Risk (months)	0	6	12	18	24
Monotherapy	803	586	476	267	109
Combination therapy	263	246	183	108	60

Fig. 1. Kaplan-Meier curves for the incidences of (A) major bleeding, (B) any bleeding (C) stroke or systemic embolism (SE), and (D) major adverse cardiac events (MACE) of entire study population according to monotherapy (NOAC only) or combination therapy (NOAC and APT).

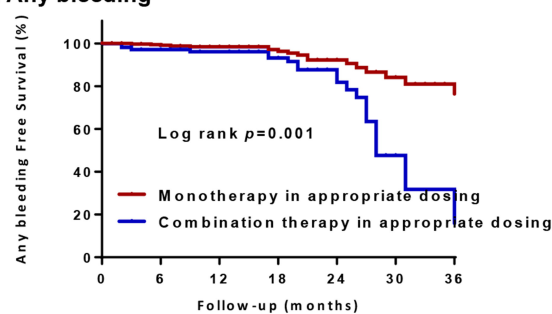
Table 3. Comparison according to the dose of NOACs.

	Overall (n = 632)	Monotherapy (n = 141)	Combination therapy (n = 491)	p-value
Over-dosage	43 (4.0)	35 (4.4)	8 (3.0)	0.343
Appropriate dosage	530 (49.6)	422 (52.5)	108 (40.9)	0.001
Under-dosage	482 (45.1)	347 (43.2)	135 (51.1)	0.024
Dabigatran	227 (21.3)	137 (17.0)	90 (34.1)	
Over-dosage	11 (4.8)	8 (5.8)	3 (3.3)	0.390
Appropriate dosage	143 (63.0)	96 (70.1)	47 (52.2)	0.006
Under-dosage	64 (28.2)	33 (24.1)	31 (34.4)	0.090
Rivaroxaban	380 (35.6)	290 (36.1)	90 (34.1)	
Over-dosage	19 (5.0)	16 (5.5)	3 (3.3)	0.406
Appropriate dosage	123 (32.4)	101 (34.8)	22 (24.4)	0.066
Under-dosage	238 (62.6)	173 (59.7)	65 (72.2)	0.031
Apixaban	461 (43.2)	377 (46.9)	84 (31.8)	
Over-dosage	13 (2.8)	11 (2.9)	2 (2.4)	0.788
Appropriate dosage	264 (57.3)	225 (59.7)	39 (46.4)	0.026
Under-dosage	180 (39.0)	141 (37.4)	39 (46.4)	0.125

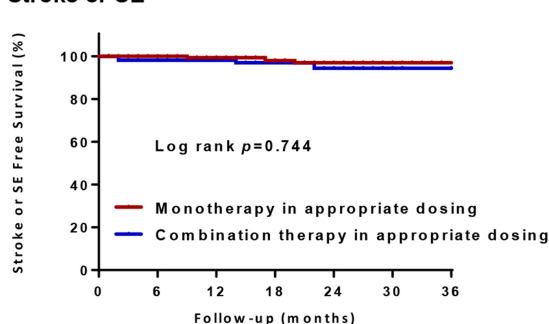
NOAC, non-vitamin K oral anticoagulants.

A. Major bleeding

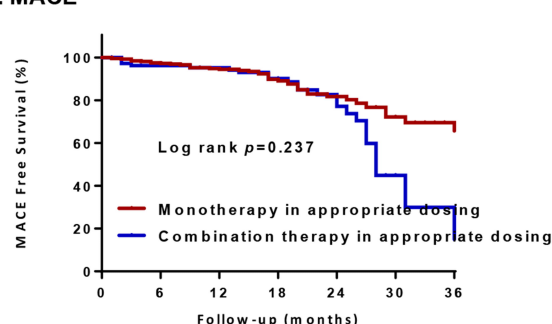
Number at Risk (months)	0	6	12	18	24
Monotherapy	421	303	238	132	58
Combination therapy	118	109	87	54	32

B. Any bleeding

Number at Risk (months)	0	6	12	18	24
Monotherapy	421	303	238	132	58
Combination therapy	118	109	87	54	30

C. Stroke or SE

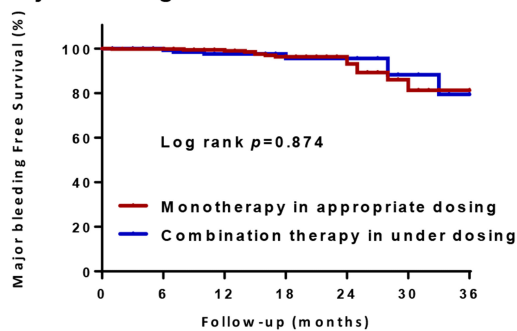
Number at Risk (months)	0	6	12	18	24
Monotherapy	421	303	238	132	59
Combination therapy	118	109	87	54	32

D. MACE

Number at Risk (months)	0	6	12	18	24
Monotherapy	421	303	236	132	58
Combination therapy	118	109	87	53	30

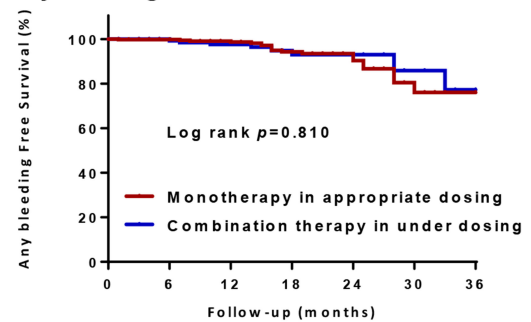
Fig. 2. Kaplan-Meier curves for the incidences of (A) major bleeding, (B) any bleeding (C) stroke or systemic embolism (SE), and (D) major adverse cardiac events (MACE) of patients with appropriate dosing according to monotherapy (NOAC only) or combination therapy (NOAC and APT).

A. Major bleeding



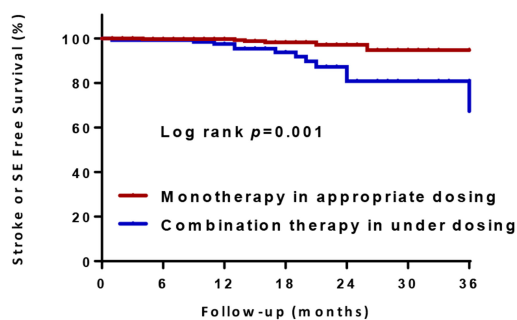
Number at Risk (months)	0	6	12	18	24
Monotherapy	421	303	238	132	58
Combination therapy	134	127	98	49	26

B. Any bleeding



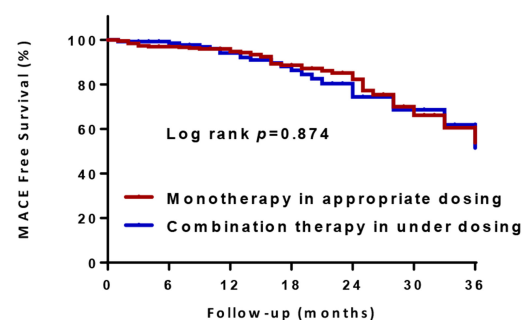
Number at Risk (months)	0	6	12	18	24
Monotherapy	421	303	238	132	58
Combination therapy	134	127	98	49	26

C. Stroke or SE



Number at Risk (months)	0	6	12	18	24
Monotherapy	421	303	238	132	59
Combination therapy	134	127	98	49	25

D. MACE



Number at Risk (months)	0	6	12	18	24
Monotherapy	421	303	236	132	58
Combination therapy	134	127	98	49	25

Fig. 3. Kaplan-Meier curves for the incidences of (A) major bleeding, (B) any bleeding (C) stroke or systemic embolism (SE), and (D) major adverse cardiac events (MACE) of some patients according to appropriate dosing monotherapy (NOAC only) or under dosing combination therapy (NOAC and APT).

Numerous studies have demonstrated that APT in patients with AF was inferior or not superior to OACs in terms of bleeding risk or benefit in stroke prevention [15]. Therefore, APT is no longer recommended as a treatment for stroke prevention in patients with AF [16,17]. However, many patients with AF have risk factors for cardiovascular events [8]. So APT is often administered in combination with NOACs in clinical settings. Combination therapy was administrated to 25.4% of the patients in this study. This was similar to other real-world registries [18,19] and randomized trials [20–23]. However, contrary to the results of this study, Ruiz *et al.* [24] reported that the use of combination therapy in AF patients initiating NOAC treatment was uncommon, at 6.1%. And 12.5% of the patients were treated with APT in addition to OACs in the GARFIELD-AF registry [25]. This finding was explained by the baseline characteristics of the enrolled patients. The study by Ruiz *et al.* [24] excluded patients with established indications for concomitant APT and the GARFIELD-AF registry included patients who had taken vitamin K antagonist.

In our study, patients taking combination therapy had higher bleeding event rates and no significant difference in stroke/SE events and MACE, consistent with previous findings. The combination of OACs and APT drugs increases the bleeding potential. Meta-analysis and observational studies demonstrated an increased risk of bleeding and no additional benefit for stroke prevention in patients given combination therapy [18,19,24,26]. Patients with combination therapy had higher incidences of major bleeding as well as stroke/SE, compared to those given monotherapy in the Fushimi AF Registry [11]. In a sub-analysis of the GARFIELD-AF registry [25], the patients treated with OACs plus APT experienced a higher incidence of adverse outcomes during the observation period. In another study similar to our study, the use of concomitant APT was not associated with lower rates of ischemic events or death, whereas there was an increased risk of bleeding. Although several studies demonstrated that APT for the secondary prevention of cardiovascular events improved clinical outcomes [27,28], the additional efficacy of APT was not demonstrated and less clear in AF patients receiving

OACs. Also, combination therapy has been mainly investigated in patients with AF who had undergone percutaneous coronary intervention (PCI). In the AFIRE trial [29], as in our study, patients with remote (>12 months) history of PCI who treated with NOAC monotherapy group demonstrated superior for safety than the combination (NOAC plus APT) therapy, and the study was terminated early. Additionally, a recent review article on antithrombotic therapy after PCI in Asians with AF reported that OAC monotherapy is reasonable if it exceeds 1 year [30]. These reports could support our findings. Our study could provide better assistance in decision making in the real practice.

In this study, approximately 45% of the patients were prescribed an under-dosage of NOAC. In the USA, 83.7% of the patients were prescribed the recommended dosage of NOACs, whereas 12.0% of the patients received an under-dosage of NOACs [31]. In the Korean National Health Insurance Service database, 51.9% of the patients were prescribed an under-dosage of NOAC [12]. Additionally, In Japan, 50% of the patients receiving reduced-dose NOACs were prescribed an under-dosage of NOAC [32]. Underdosing with NOACs in Asians was more common than in Westerners. Physicians tend to be more anxious about the side effects of bleeding than the risk of stroke [33]. In particular, Asians have a small body size and are known to have a high frequency of cerebral hemorrhages and gastrointestinal bleeding associated with the use of OACs, so physicians in Asia tend to administer an under-dosage of NOACs [34]. Also, concomitant APT use was associated with under-dosage NOAC prescriptions. According to observational studies [35], the combination group had a higher proportion of under-dosage prescriptions than the monotherapy group, consistent with our findings. Recently, adverse clinical outcomes in patients prescribed under-dosages of NOACs have been reported from real-world data [12]. In the ORBIT-AF II registry, compared to the patients appropriately dosed with NOACs, patients given under-dosages of NOAC showed higher adverse event rates [13]. Our results demonstrated that under-dosed patients in the combination group showed increased stroke/SE events compared to appropriately dosed patients in the monotherapy group. The appropriate use of NOACs is emerging as an important issue.

There were several limitations to this study. First, the data in the study were acquired from electronic medical records, retrospectively. Due to the limitation of a retrospective study, it is possible that the clinical results were measured lower than the actual incidence rate. However, this would not have affected the comparison of the results in the monotherapy group and the combination group. Second, the usage of APT was based on each physicians' preference and the patient's baseline characteristics and it also might affect the physician's choice of the dosage of NOACs by the previous history of bleeding or thromboembolic events. It is an inherent limitation of retrospective re-

search. The bias was already included in the study design. The baseline characteristics and all clinical outcomes were made only through the medical records. There was a lack of information on lifestyle, social habits: drinking and smoking, or using concomitant drugs, such as NSAIDs. Finally, this was a single-center retrospective study with relatively small number of the patients with combination therapy and the variable baseline characteristics in both groups. The results cannot be generalized, and a further prospective study was needed to confirm the safety for the combination therapy.

5. Conclusions

Patients taking combination therapy had higher incidences of any bleeding compared to AF patients taking monotherapy, whereas no significant difference was seen in stroke prevention. Many patients were prescribed under-dosages of NOAC, especially in the combination therapy group. Careful evaluation of the indications for APT in patients with AF who are also taking NOACs is warranted, and a future randomized comparison study is needed.

Abbreviations

AF, atrial fibrillation; APT, antiplatelet agents; CrCl, creatinine clearance; MACE, major adverse cardiac events; HR, hazard ratio; NOACs, non-vitamin K antagonist oral anticoagulants; PAF, paroxysmal AF; PCI, percutaneous coronary intervention; SE, systemic embolic; TIA, transient ischemic attack.

Author contributions

All authors contributed and participated in the preparation of the manuscript and research steps in the present study as follows: Conception and Design and Supervision—YRK. Acquisition of data—SK, YRK. Analysis of data and Writing of original draft—DGS. Reading, Revising and Final approval for submission—All.

Ethics approval and consent to participate

This study protocol was approved by Incheon St. Mary's Hospital Institutional Review Board/2020-4026-0001.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://www.imrpress.com/journal/RCM/23/1/10.31083/j.rcm2301002>.

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