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Concomitant Use of NSAIDs or SSRIs with NOACs Requires Monitoring for Bleeding

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Purpose: Non-vitamin K antagonist oral anticoagulants (NOACs) are widely used in patients with atrial fibrillation (AF) because of their effectiveness in preventing stroke and their better safety, compared with warfarin. However, there are concerns for an increased risk of bleeding associated with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) or selective serotonin reuptake inhibitors (SSRIs) with NOACs. In this study, we aimed to evaluate the risk of bleeding events in individuals taking concomitant NSAIDs or SSRIs with NOACs after being diagnosed with AF.

Materials and Methods: A nested case-control analysis to assess the safety of NSAIDs and SSRIs among NOAC users with AF was performed using data from Korean National Health Insurance Service from January 2012 to December 2017. Among patients who were newly prescribed NOACs, 1233 cases hospitalized for bleeding events were selected, and 24660 controls were determined.

Results: The risk of bleeding events was higher in patients receiving concomitant NSAIDs [adjusted odds ratio (aOR) 1.41; 95% confidence interval (CI) 1.24–1.61] or SSRIs (aOR 1.92; 95% CI 1.52–2.42) with NOACs, compared to no use of either drug, respectively. The risk of upper gastrointestinal bleeding was higher in patients receiving concomitant NSAIDs or SSRIs without proton pump inhibitors (PPIs) (NSAIDs: aOR 2.47; 95% CI 1.26–4.83, SSRI: aOR 10.8; 95% CI 2.41–2.48) compared to no use.

Conclusion: When NSAIDs or SSRIs are required for NOAC users with AF, physicians need to monitor bleeding events and consider the use of PPIs, especially for combined use of both drugs or when initiating NOACs treatment.

Key Words: Non-vitamin K antagonist oral anticoagulants, atrial fibrillation, nested case-control study, hemorrhages, drug interactions

INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs), introduced to the market in 2010, have been used to treat patients with atrial fibrillation (AF) instead of warfarin. About 85% of patients with AF take oral anticoagulants (OACs),[1] because treatment with OACs markedly decreases the risk of ischemic stroke in patients with AF.[2] Before the launch of NOACs, warfarin was the only OAC used for patients with AF.[1] Because of the disadvantages of using warfarin, including a narrow therapeutic range, interaction with various foods and drugs, and the requirement of frequent monitoring for bleeding,[3] NOACs have been preferred in clinical settings.

However, although to lesser degrees than warfarin, NOACs have also been reported to pose a risk of bleeding complications, which may be influenced by pharmacokinetic or pharmacodynamic interactions. Whereas an increased risk of bleeding in warfarin has been well studied, there is still insufficient evidence about the risk of bleeding events associated with drug-drug interactions with NOACs. To date, several studies have assessed the numbers of potentially interacting drugs on the risk of composite bleeding events in patients using NOAC using databases in Taiwan,[4] the United Kingdom,[5] and German nursing homes.[6] However, interactions with drugs inhibiting platelet aggregation, including non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs), were not as-

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sessed[4] or showed conflicting results with previous studies.[5,6]

NSAIDs are commonly used in short- or long-term treatment for several indications, including osteoarthritis and rheumatic diseases. A Danish study reported that 21% of NOACs users took concomitant NSAIDs,[7] and a post hoc analysis of the RE-LY trial revealed an increased risk of major bleeding associated with NSAIDs in NOAC users.[8] SSRIs are a first-line pharmaceutical treatment for major depressive disorder and anxiety disorders and have relatively favorable safety profiles. However, studies have reported an increased risk of intracranial[9] or gastrointestinal (GI) hemorrhage[10] associated with use of SSRIs. Furthermore, combined use of NSAIDs and SSRIs concomitantly with NOACs may pose an additional increase in the risk of bleeding. One study has shown that SSRIs combined with NSAIDs increases the risk of intracranial bleeding,[11] and a meta-analysis has reported a synergistic effect on GI bleeding with combined use of NSAIDs and SSRIs.[12] To date, however, population-based studies quantifying the degree of risk of bleeding associated with concomitant use of NSAIDs or SSRIs, especially for combined use of the two drugs, remain scarce.

Concerning the risk of upper GI bleeding with NOACs, using proton pump inhibitors (PPIs) when prescribing NOACs has been recommended in the 2018 European Heart Rhythm Association guideline, especially in patients with a history of GI bleeding or ulcer and patients requiring concomitant use of antiplatelet therapy.[13] However, real-world data on the gastroprotective effect in patients with NOACs, especially with concomitant use of NSAIDs or SSRIs, is limited.

Accordingly, this study's objective was to evaluate the risk of bleeding events in individuals taking concomitant NSAIDs or SSRIs with NOACs after being diagnosed with AF and to identify the risk of bleeding events. The second goal was to assess the risk of upper GI bleeding after the use of NSAIDs or SSRIs combined with PPIs. Finally, we performed subgroup analyses to determine high-bleeding risk groups.

MATERIALS AND METHODS

Data source

This study used National Health Information Database (NHIS-2019-1-402) made by National Health Insurance Service (NHIS), a single-payer organization that is mandatory for all residents in Korea. For this reason, the NHIS obtains information on patient demographics, insurers' payment coverage, medical use/transactions, diagnoses, claims of procedures, and inpatient/outpatient prescriptions. All diagnoses are coded according to the international classification of disease, 10th revision, clinical modification (ICD-10 CM) established by the World Health Organization. This study was approved by the Chung-Ang University Bioethics Committee (Approval Number 1041078-201903-HR-097-01).

Study population

We conducted a nested case-control analysis among patients with AF (ICD-10, I48) who were first prescribed NOACs during the study period from January 1, 2013, to December 31, 2017. NOACs included in this study were apixaban, rivaroxaban, edoxaban (factor Xa inhibitors), and dabigatran (direct thrombin inhibitor). The date of the first NOAC prescription after AF was set as the cohort entry. For each cohort population, at least 1 year of look-back period was applied before the first NOAC prescription (2012.1.1.–2017.12.31.) to define new-users of NOACs without any history of bleeding events. We also excluded patients diagnosed with cancer at least once and those who switched from NOACs to warfarin during the study period. We determined the cohort endpoint as 1) hospitalization or emergency department visit due to bleeding, 2) death, or 3) end of the study period, whichever came first.

In order to define an NOAC treatment episode, we allocated a grace period of 14 days. If a new prescription started less than 14 days from the end of the previous prescription and days of supply, we defined the two prescriptions as the same treatment episode, which began from the date of the previous prescription and ended with the days of supply of the new prescription. We defined the first NOACs treatment episode at cohort entry as the "incident episode" and the NOACs episode after exiting the incident episode without hospitalization or emergency department visit for bleeding as the "prevalent episode". Thus, each cohort individual had only one incident episode and potentially several prevalent episodes.

Definition of cases and controls

Cases were defined as patients that underwent hospitalization or emergency department visit for major bleeding events. The major bleeding events were categorized as upper GI bleeding, lower GI bleeding, intracranial bleeding, and other bleedings, including urinary tract bleeding, airway bleeding, and others, based on previous reports in the literature (Supplementary Table 1, only online).[4,6,14] For each case, up to 20 controls at risk of the bleeding event were randomly selected by age (±5 years), sex, episode status, and duration from diagnosis of AF to the prescription of NOACs (±1 year) using risk-set sampling. In the risk-set sampling, patients could serve as controls for multiple cases, and patients were eligible to be selected as controls before becoming a case. For each control, an index date was assigned to have the same length of follow-up as that for a corresponding case. This approach resembles Cox regression with time-varying covariates and is reported to produce comparable and unbiased estimates of hazard ratios compared by Cox regression on the full cohort, with superior computational efficiency when studying time-dependent exposure, such as drug-drug interactions.[15,16]

Exposure

Comedication was assessed based on potential drug interactions

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with OACs reported in the literature.[6,8,17] We included NSAIDs (aceclofenac, indomethacin, sulindac, diclofenac, acemetacin, etodolac, proglumetacin, ketorolac, piroxicam, lornoxicam, meloxicam, ibuprofen, naproxen, ketoprofen, flurbiprofen, tiaprofenic acid, oxaprozin, ibuproxam, dexibuprofen, dexketoprofen, nabumetone, nimesulide, morniflumate, mefenamic acid, celecoxib, etoricoxib, and polmacoxib) and SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine, and escitalopram). To examine the protective effect of PPIs on risk of upper GI bleeding, we included PPIs (omeprazole, lansoprazole, pantoprazole, dexlansoprazole, and esomeprazole) as another exposure variable. Exposure was considered to have occurred if NSAIDs, SSRIs, or PPIs overlapped during a continuous NOAC treatment episode for at least 3 days.[18] We performed sensitivity analysis for definition of exposure as at least 1-, 7-, 14-, and 30-days overlap within the NOAC episode.

Covariates and comorbidities

We considered covariates, including demographic characteristics (age, sex), episode status, insurance, inpatient and outpatient hospital visits less than 1 year before the index date, comedication, Charlson comorbidity index,[19] HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history, labile international normalized ratios (INRs), elderly, drug consumption/alcohol abuse][20] score, and CHA_2DS_2-VASc (congestive heart failure/left ventricular dysfunction, hypertension, age, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, sex) score, and comorbidities. For Charlson comorbidity index scores, we assigned 1 point each for myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, and diabetes without complications; 2 points each for hemiplegia or paraplegia, renal disease, diabetes with chronic complications, and cancer; 3 points each for moderate or severe liver disease, and 6 points each for metastatic solid tumor and AIDS/HIV. CHA_2DS_2-VASc scores were calculated by assigning 1 point each for congestive heart failure, hypertension, age 65–74 years, diabetes mellitus, and vascular disease (myocardial infarction, peripheral arterial disease, arteriosclerosis of aorta) and 2 points each for age ≥75 years and one of stroke/transient ischemic attack/thromboembolism.[19] HAS-BLED scores were calculated by assigning 1 point each for hypertension, abnormal renal/liver function, stroke, bleeding history, old age, drug consumption (NSAIDs or antiplatelets), and alcohol abuse.[20] The codes used are shown in Supplementary Table 1 (only online).

Statistical analysis

We determined the descriptive statistics of demographics and incidence rate of bleeding events per 100 person-years according to the overall bleeding events, sex, and episode status information provided in the NHIS database. Continuous variables were summarized as means with standard deviations, and categorical variables were expressed as numbers and percentages. The chi-square test was performed for comparisons of categorical variables. Comparison of continuous variables was performed using the independent t-test.

We calculated adjusted odds ratios (aOR) of bleeding events and their 95% confidence intervals (CI) associated with the concomitant use of study drugs with NOACs and considering potential confounders using a conditional logistic regression model. We assessed the effect of NSAIDs or SSRI individually, as well as the combined effect of NSAIDs and SSRIs with NOACs.

To determine variables to be adjusted, we considered differences between two groups with $p<0.2$ in univariate analysis, along with variables, including comedications (beta-blockers, calcium channel blockers, angiotensin II receptor antagonists, statins, and diuretics) and comorbidities (myocardial infarction, dementia, and liver/renal disease) reported in previous studies.

Additionally, subgroup analyses were performed to consider patients with HAS-BLED scores ≥3 or <3 points. HAS-BLED score is a practical tool with which to assess the bleeding risk of patients with AF. Subgroup analysis with statistical tests for interaction according to age group, sex, and NOAC treatment episode status was performed to investigate whether the association of concomitant NSAIDs or SSRIs use with NOACs and bleeding events differed significantly between subgroups.

RESULTS

A total of 187410 patients with AF who were prescribed NOACs at least once were identified from January 2013 to December 2017. Of the 57609 patients determined to be new NOAC users, a total of 28905 patients were excluded because of bleeding history (19863), diagnosis with cancer (7135), and history of warfarin use (1907), leaving a total of 28704 (Fig. 1). Among the cohort of NOAC new users, the incidence rate of bleeding events was 3.68 (95% CI 100 per person-year) (Supplementary Table 2, only online), and the number of bleeding events that occurred was 1233.

A total of 1233 cases and 24660 controls were determined from new NOAC users (Fig. 1). The mean ages for cases and controls were 76.0±8.93 and 76.6±9.08 years, respectively (Table 1). Females comprised 53.9% of both cases and controls, and the incident episode was 72.7%. With regard to concomitant drugs, more cases received NSAIDs (47.0% vs. 41.6%, $p<0.0001$) and SSRIs (7.8% vs. 4.2%, $p<0.0001$) than the controls. In terms of comorbidity, cases had significantly more diseases, including myocardial infarction, congestive heart failure, cerebrovascular disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, and diabetes without chronic complications, compared with controls. Charlson comorbidity index, HAS-BLED, and CHA_2DS_2-VASc scores were significantly higher in cases than controls ($p<0.001$).

The aORs of concomitant NSAIDs and SSRIs with NOACs af-

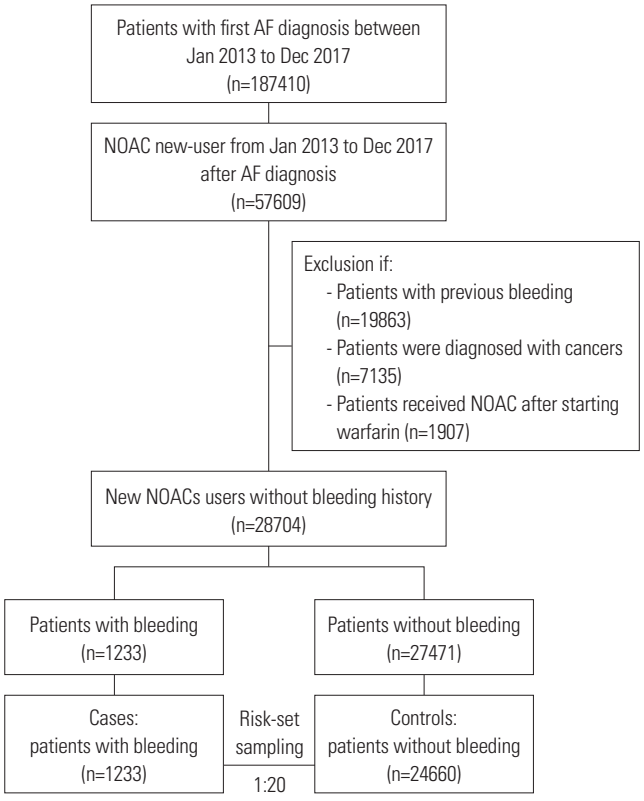

Fig. 1. Flowchart of selection of the study population. AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant.

ter adjusting for potential confounders were 1.41 (95% CI 1.24–1.61) and 1.92 (95% CI 1.52–2.42), compared with non-NSAIDs and SSRIs, respectively. When assessing the effects of the combined use of NSAIDs and SSRIs, compared with non-use of either drug, the aORs of overall major bleeding events associated with using only NSAIDs, only SSRIs, and both NSAIDs and SSRIs during NOAC episode were 1.39 (95% CI 1.22–1.59), 1.78 (95% CI 1.28–2.49), and 2.67 (95% CI 1.95–3.66), respectively (Table 2). Sensitivity analyses applying several different definitions of overlapping durations of concomitant drug exposures showed similar results compared with the main analysis (Supplementary Table 3, only online).

Results of analysis according to each bleeding event are shown in Table 3. The aORs of upper GI bleeding were not statistically significant when NSAIDs or SSRIs were used with PPIs. However, when used without PPIs, aORs for upper GI bleeding were 2.47 (95% CI 1.26–4.83) for NSAIDs only and 10.8 (95% CI 2.41–48.1) for SSRIs only, although using both NSAIDs and SSRI did not show a significant increase in the aOR.

When we assessed the effect of individual drugs, NSAIDs showed significantly increased risks for lower GI bleeding (aOR 1.33; 95% CI 1.07–1.66), urinary tract bleeding (aOR 1.47; 95% CI 1.19–1.82), and airway bleeding (aOR 2.15; 95% CI 1.32–3.48), and SSRIs showed significantly increased risks for intracranial bleeding (aOR 2.69; 95% CI 1.57–4.59) and urinary tract bleeding (aOR 2.37; 95% CI 1.63–3.42) (Supplementary Table 4, only online).

Table 1. Characteristics of Cases and Controls at Index Date

Characteristic	Case (n=1233)	Control (n=24660)	*p* value
Age	76.0±8.93	76.6±9.08	
Female sex	664 (53.9)	13280 (53.9)	
NOAC episode status*			
Incident episode	896 (72.7)	17920 (72.7)	
Prevalent episode	337 (27.3)	6740 (27.3)	
Comedication			
NSAIDs	580 (47.0)	10261 (41.6)	<0.001
SSRIs	96 (7.8)	1034 (4.2)	<0.001
PPIs	425 (34.5)	8712 (35.4)	0.506
Comorbidity			
Myocardial infarction	75 (6.1)	1132 (4.6)	0.016
Congestive heart failure	600 (48.7)	10465 (42.4)	<0.001
Peripheral vascular disorders	213 (17.3)	4901 (19.9)	<0.001
Cerebrovascular disease	574 (46.6)	8952 (36.3)	<0.001
Dementia	258 (20.9)	4728 (19.2)	0.123
Rheumatic disease	243 (19.7)	4418 (17.2)	0.105
Peptic ulcer disease	324 (26.3)	4670 (18.9)	<0.001
Mild liver disease	219 (17.8)	3553 (14.4)	0.001
Moderate or severe liver disease	598 (48.5)	10377 (42.1)	<0.001
Diabetes without complications	455 (36.9)	7506 (30.4)	<0.001
Diabetes with complications	134 (10.9)	2618 (10.6)	0.778
Renal disease	63 (5.1)	961 (3.9)	0.032
Hypertension	1049 (85.1)	17979 (72.9)	<0.001
CHA_2DS_2-VASc score	4.64±1.7	4.35±1.86	<0.001
HAS-BLED score	3.48±1.28	2.85±1.21	<0.001
Charlson comorbidity score	4.73±2.99	4.07±3.22	<0.001

NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; PPIs, proton pump inhibitors; NOAC, non-vitamin K antagonist oral anticoagulant.
Data are presented as mean±standard deviation or n (%).
*Incident episode, first NOACs treatment episode at cohort entry; prevalent episode: a NOACs episode after exiting the incident episode without hospitalization or emergency department visit for bleeding.

Table 4 lists the risks of bleeding events in subgroups according to HAS-BLED score, age, sex, and episode status. We found no significant difference in risk associated with HAS-BLED score, age groups, and sex. The aORs of bleeding events for concomitant use of both NSAIDs and SSRIs were 2.69 (95% CI 1.92–3.76) in patients with HAS-BLED score≥3 and 1.54 (95% CI 0.47–5.07), compared with non-use of either drugs (*p* interaction=0.75). The aORs of bleeding event associated with use of NSAIDs or SSRIs were higher among incident than prevalent NOAC episodes (aOR of using both NSAIDs and SSRIs: 4.27 (95% CI 2.96–6.16) versus 1.18 (95% CI 0.59–2.39) (*p* for interaction=0.03).

In subgroup analysis of individual use of study drugs, aORs of bleeding associated with using NSAIDs or SSRI during an incident NOAC episode were 1.74 (95% CI 1.49–2.03) and 2.09 (95% CI 1.59-2.75), respectively (Supplementary Table 5, only online).

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DISCUSSION

This study investigated the safety of NOAC users with AF receiving concomitant NSAIDs or SSRIs. The risk of overall bleeding events increased in those given concomitant NSAIDs or SSRIs, compared with those not using NSAIDs or SSRIs, respectively.

Table 2. Risk of Bleeding Events Associated with Concomitant NSAIDs/SSRIs with NOACs

	Case (n=1233)	Control (n=24660)	Crude OR (95% CI)	Adjusted OR (95% CI)*
NSAIDs	556 (45.1)	9503 (38.5)	1.36 (1.20–1.53)	1.41 (1.24–1.61)
SSRIs	95 (7.7)	1031 (4.2)	1.92 (1.54–2.39)	1.92 (1.52–2.42)
No use	632 (51.3)	14644 (59.4)	Ref	Ref
NSAIDs only	506 (41.0)	8985 (36.4)	1.36 (1.20–1.55)	1.39 (1.22–1.59)
SSRIs only	45 (3.6)	513 (2.1)	2.10 (1.53–2.88)	1.78 (1.28–2.49)
Both NSAIDs and SSRIs	50 (4.1)	518 (2.1)	2.32 (1.72–3.15)	2.67 (1.95–3.66)

OR, odds ratio; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; NOAC, non-vitamin K antagonist oral anticoagulant.
*Adjusted for demographic characteristics, comedications (beta-blockers, calcium channel blockers, angiotensin II receptor antagonists, statins, diuretics), and comorbidities (myocardial infarction, dementia, liver/ renal disease).

Table 3. Risk of Each Bleeding Event with Concomitant NSAIDs/SSRIs with NOACs

	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)*
Upper GI bleeding (case=75, control=1500)				
No use	35 (46.7)	934 (62.3)	Ref	Ref
NSAIDs only	32 (42.7)	496 (33.1)	1.72 (1.05–2.82)	2.07 (1.20–3.56)
SSRIs only	6 (8.0)	36 (2.4)	4.45 (1.76–11.2)	4.12 (1.44–11.8)
Both NSAIDs and SSRIs	2 (2.7)	34 (2.3)	1.57 (0.36–6.80)	1.98 (0.41–9.60)
Upper GI, with PPIs (case=24, control=477)				
No use	11 (45.8)	239 (50.1)	Ref	Ref
NSAIDs only	10 (41.7)	200 (41.9)	1.09 (0.45–2.66)	1.23 (0.41–3.89)
SSRIs only	2 (8.3)	20 (4.2)	2.17 (0.45–10.5)	2.92 (0.49–7.39)
Both NSAIDs and SSRIs	1 (4.2)	18 (3.8)	1.21 (0.15–9.89)	4.34 (0.33–57.3)
Upper GI, without PPIs (case=51, control=1023)				
No use	24 (47.1)	695 (67.9)	Ref	Ref
NSAIDs only	22 (43.1)	296 (28.9)	2.15 (1.19–3.90)	2.47 (1.26–4.83)
SSRIs only	4 (7.8)	16 (1.6)	7.24 (2.25–23.3)	10.8 (2.41–48.1)
Both NSAIDs and SSRIs	1 (2.0)	16 (1.6)	1.81 (0.23–14.2)	1.19 (0.13–11.2)
Lower GI bleeding (case=437, control=8740)				
No use	228 (52.2)	5242 (60.0)	Ref	Ref
NSAIDs only	179 (41.0)	3136 (35.9)	1.31 (1.07–1.60)	1.32 (1.06–1.63)
SSRIs only	16 (3.7)	182 (2.1)	2.02 (1.19–3.43)	1.39 (0.78–2.48)
Both NSAIDs and SSRIs	14 (3.2)	180 (2.1)	1.79 (1.02–3.13)	1.76 (0.98–3.15)
Intracranial bleeding (case=233, control=4460)				
No use	121 (54.3)	2690 (60.3)	Ref	Ref
NSAIDs only	82 (36.8)	1603 (35.9)	1.14 (0.85–1.52)	1.28 (0.94–1.75)
SSRIs only	11 (4.9)	73 (1.6)	3.35 (1.73–6.48)	3.14 (1.13–6.39)
Both NSAIDs and SSRIs	9 (4.0)	94 (2.1)	2.13 (1.05–4.32)	2.91 (1.35–6.29)
Other bleedings† (case=602, control=12040)				
No use	299 (49.7)	7076 (58.8)	Ref	Ref
NSAIDs only	256 (42.5)	4447 (36.9)	1.36 (1.15–1.62)	1.51 (1.26–1.82)
SSRIs only	20 (3.3)	267 (2.2)	1.77 (1.11–.283)	1.81 (1.11–2.96)
Both NSAIDs and SSRIs	27 (4.5)	250 (2.1)	2.56 (1.69-3.87)	3.88 (2.50-6.03)

GI, gastrointestinal; OR, odds ratio; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; PPIs, proton pump inhibitors; NOAC, non-vitamin K antagonist oral anticoagulant.
*Adjusted for demographic characteristics, comedications (beta-blockers, calcium channel blockers, angiotensin II receptor antagonists, statins, diuretics), and comorbidities (myocardial infarction, dementia, liver/renal disease), †Other bleedings include urinary tract, airway, and other bleedings (Supplementary Table 1, only online).

Table 4. Subgroup Analysis on Risk of Bleeding Events Associated with NSAIDs or SSRIs Concomitant with NOACs

	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)*
HAS-BLED score				
HAS-BLED 0–2 (case=279, control=10099)				
No use	197 (70.6)	7367 (72.9)	Ref	Ref
NSAIDs only	67 (24.0)	2414 (23.9)	1.04 (0.78–1.38)	1.37 (1.10–2.14)
SSRIs only	12 (4.3)	188 (1.9)	2.39 (1.31–4.35)	2.14 (1.12–4.09)
Both NSAIDs and SSRIs	3 (1.1)	130 (1.3)	0.86 (0.27–2.73)	1.54 (0.47–5.07)
HAS-BLED 3–8 (case=954, control=14561)				
No NSAIDs or SSRIs	435 (45.6)	7277 (50.0)	Ref	Ref
NSAIDs only	439 (46.0)	6571 (45.1)	1.12 (0.98–1.28)	1.18 (1.02–1.37)
SSRIs only	33 (3.5)	325 (2.2)	1.70 (1.17–2.46)	1.66 (1.13–2.46)
Both NSAIDs and SSRIs	47 (4.9)	388 (2.7)	2.03 (1.48–2.79)	2.69 (1.92–3.76)
				p for interaction=0.75
Age groups				
<75 years (case=467, control=7982)				
No use	250 (53.5)	4799 (60.1)	Ref	Ref
NSAIDs only	188 (40.3)	2821 (35.3)	1.22 (0.84–1.36)	1.07 (0.84–1.36)
SSRIs only	15 (3.2)	194 (2.4)	1.53 (0.88–2.66)	1.19 (0.66–2.15)
Both NSAIDs and SSRIs	14 (3.0)	168 (2.1)	1.63 (0.91–2.90)	2.48 (1.31–4.70)
75 years or older (case=766, control=16678)				
No use	382 (49.9)	9845 (59.0)	Ref	Ref
NSAIDs only	318 (41.5)	6164 (37.0)	1.40 (1.14–1.64)	1.48 (1.25–1.76)
SSRIs only	30 (3.9)	319 (1.9)	2.59 (1.74–3.84)	1.95 (1.26–3.02)
Both NSAIDs and SSRIs	36 (4.7)	350 (2.1)	2.71 (1.89–3.88)	2.75 (1.88–4.02)
				p for interaction=0.52
Sex				
Male (case=569, control=11380)				
No use	308 (54.1)	7420 (65.2)	Ref	Ref
NSAIDs only	229 (40.2)	3488 (30.7)	1.67 (1.39–2.01)	1.65 (1.34–2.02)
SSRIs only	14 (2.5)	243 (2.1)	1.45 (0.83–2.51)	1.45 (0.82–2.58)
Both NSAIDs and SSRIs	18 (3.2)	229 (2.0)	2.07 (1.25–3.42)	2.47 (1.45–4.20)
Female (case=664, control=13280)				
No use	324 (48.8)	7224 (54.4)	Ref	Ref
NSAIDs only	277 (41.7)	5497 (41.4)	1.14 (0.96–1.36)	1.18 (0.98–1.42)
SSRIs only	31 (4.7)	270 (2.0)	2.62 (1.77–3.89)	2.06 (1.32–3.20)
Both NSAIDs and SSRIs	32 (4.8)	289 (2.2)	2.46 (1.68–3.60)	3.44 (2.27–5.21)
				p for interaction=0.17
Episode status				
Incident episode (case=896, control=17920)				
No use	435 (48.5)	10509 (58.6)	Ref	Ref
NSAIDs only	391 (43.6)	6692 (37.3)	1.49 (1.29–1.73)	1.68 (1.43–1.97)
SSRIs only	30 (3.3)	363 (2.0)	2.06 (1.40–3.04)	1.66 (1.09–2.51)
Both NSAIDs and SSRIs	40 (4.5)	356 (2.0)	2.85 (2.02–4.02)	4.27 (2.96–6.16)
Prevalent episode (case=337, control=6740)				
No use	197 (58.5)	4135 (61.4)	Ref	Ref
NSAIDs only	115 (34.1)	2293 (34.0)	1.06 (0.83–1.36)	0.98 (0.75–1.27)
SSRIs only	15 (4.5)	150 (2.2)	2.15 (1.23–3.77)	1.92 (1.06–3.51)
Both NSAIDs and SSRIs	10 (3.0)	162 (2.4)	1.31 (0.68–2.54)	1.18 (0.59–2.39)
				p for interaction=0.03

CI, confidence interval; OR, odds ratio; NSAIDs, non-selective non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; NOAC, non-vitamin K antagonist oral anticoagulant.
*Adjusted for demographic characteristics, risk factors for comedications thought to affect risk (beta-blockers calcium channel blockers, angiotensin II receptor antagonists, statins, diuretics), and comorbidities (myocardial infarction, dementia, liver/renal disease.

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We found that the use of both NSAIDs and SSRIs within NOACs treatment episode showed higher risks of overall major bleeding events, compared with non-use of either drug. We also observed that the risk of upper GI bleeding associated with using NSAIDs or SSRIs was lower when using PPIs and that the risk of bleeding associated with concomitant use of NSAIDs or SSRIs was higher in an incident NOAC episode.

Our results of an increased risk of bleeding events associated with concomitant NSAIDs use with NOAC are in line with previous population-based studies.[6,8,21] A recent study using a UK database reported no significant increase in concomitant NSAIDs use with NOAC.[5] A higher prevalence of concomitant NSAIDs use with NOAC than previous studies (38.4% in present study; 5.2% in German study[6] and 1.4% in UK population[5]) might be an explanation for the difference. In the present study, concomitant use of SSRIs with NOAC showed significantly increased risk of overall major bleeding events, which is consistent with recent studies on potentially interacting drugs with NOAC.[5,6]

The mechanism of NSAIDs-induced bleeding is known to be due to reduced production of thromboxane A2 by inhibiting cyclooxygenase-1 and inhibition of mucosal-protective effects, notably in the GI tract, by preventing the synthesis of prostaglandins.[22] SSRIs are known to inhibit platelet aggregation and also to directly decrease platelet adhesion to both collagen and fibrinogen.[23] In addition, a potential increased OAC effect via inhibition of CYP450 by SSRIs has been reported.[24]

This study found that, although use of concomitant NSAIDs within NOAC episodes was associated with a significant increase in upper GI bleeding, using NSAIDs with PPIs showed no significant increase of the risk. Concomitant SSRIs with NOAC, especially when used without PPIs, showed marginally increased risk of upper GI bleeding. SSRIs may increase gastric acid secretion and increase the risk of ulcer formation and GI bleeding.[25] To prevent upper GI bleeding, recent clinical guidelines[13] have recommended using PPIs in NOAC users with underlying gastric ulcers or using antiplatelet agents. When NSAIDs or SSRIs are required for NOAC users with AF, use of PPIs to minimize risk of upper GI bleeding needs to be considered.

In our study, concomitant use of NSAIDs was associated with an increased risk of lower GI bleeding in NOAC users. Lanas, et al.[21] also showed that concomitant NSAIDs with NOACs increased the risk of lower GI bleeding. Because NSAIDs can damage the mucosa of the small intestine and even the colon,[26] the increased risk of lower GI bleeding associated with NSAIDs use needs attention for AF patients who use NOACs. Whereas concomitant NSAIDs showed no significant increase, SSRIs showed significantly increased risk of intracranial bleeding in NOAC users. Although combined use of NSAIDs and SSRIs showed significant increases in intracranial bleeding, the result might be attributed to the effect of SSRIs. Consistently with our data, several studies have demonstrated that intracranial bleeding occurs in NOAC users given concomitant SSRIs.[27,28] Both NSAIDs and SSRIs showed significantly increased risks of urinary tract bleeding. Until now, there have been some case reports of NOAC-induced nephropathy.[29,30] Further population-based studies examining the association between potential interacting drugs of NOAC and risk of urinary tract bleeding are needed.

In the present study, the risk of bleeding events associated with concomitant NSAIDs or SSRIs with NOACs was higher in incident NOAC episodes than prevalent episodes. An increased risk of bleeding events early in the course of anticoagulant therapy has also been reported in a previous study.[31] More cautious use of concomitant NSAIDs or SSRIs use and attention for bleeding events are needed for patients undergoing initial NOAC treatment.

With warfarin, physicians recommend dose control, frequent monitoring, and bleeding assessment when prescribing concomitant drugs, such as NSAIDs.[13,32] Although NOACs may increase the risk of bleeding events, the use of NOACs is suggested in guidelines, and there is insufficient evidence about interactions with concomitant drugs.[13] For these reasons, physicians may have given less attention to the risk of concomitant drugs in prescribing NOACs, and they need to consider concomitant drugs when prescribing NOACs.

Our study has several strengths. This study included the entire Korean population covered under the NHIS, which is a well-established database. Therefore, our findings have high generalizability and reflect real world practice. Second, previous studies considered potentially interacting drugs on risk as composite bleeding events. We identified individual bleeding events, including upper GI, lower GI, intracranial, and other bleedings. Third, we performed subgroup analyses according to age groups, HAS-BLED score, and episode status to determine high-risk groups of bleeding associated with comedications with NOACs, which would be useful for decision making in additional treatment for AF patients with NOAC therapy in clinical practice.

However, this study needs to be interpreted considering several limitations. We did not sufficiently consider clinical test results that may indicate potential risks, such as blood pressure, INR levels, and creatinine clearance. However, HAS-BLED and CHA_2DS_2-VASc scores related to bleeding risk were calculated as comorbidities, such as hypertension and abnormal renal/liver function, less than 1 year before the bleeding events using ICD-10 code. Nevertheless, we applied ICD-10 codes because previous studies have yielded these definitions as claim data. Second, indications or unmeasured potential confounders may have remained. The NHIS does not capture the effect of the use of over-the-counter medications (or smoking behavior) on bleeding events. In Korea, drugs related to increased bleeding risk, including NSAIDs and aspirin, are given over the counter, which could have led to underestimations in our results. Third, we did not examine bleeding risk according to individual types of NOACs, NSAIDs, and SSRIs, or dose-response. Finally, actual adherence was unknown, as we used claim data.

In conclusion, when prescribing NSAIDs or SSRIs for NOAC users with AF, physicians need to monitor bleeding events, es-

pecially for combined use of both drugs or when initiating NOACs treatment. In addition, when prescribing NSAIDs or SSRIs, use of PPIs to prevent upper GI bleeding needs to be considered.

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