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.³ 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-
Use of NSAID or SSRI with NOAC Increases Bleeding

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). 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.

Exposure
Comedication was assessed based on potential drug interactions.
with OACs reported in the literature.\textsuperscript{5,8,17} We included NSAIDs (acetaminophen, indomethacin, sulindac, diclofenac, acetametacin, etodolac, proglumetacin, ketorolac, piroxicam, lornoxicam, meloxicam, ibuprofen, naproxen, ketoprofen, flurbiprofen, tiaprofenic acid, oxaprozin, ibuprofen, dexibuprofen, dexketoprofen, nabumetone, nimesulide, morniflumate, meloxicam, 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.\textsuperscript{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, comorbidities, Charlson comorbidity index,\textsuperscript{19} HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history, labile international normalized ratios (INRs), elderly, drug consumption/alcohol abuse]\textsuperscript{20} score, and CHA\textsubscript{2}-DS\textsubscript{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\textsubscript{2}-DS\textsubscript{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 the aorta) and 2 points each for age ≥75 years and one of stroke/transient ischemic attack/thromboembolism.\textsuperscript{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.\textsuperscript{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 comedinations (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 incidence 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\textsubscript{2}-DS\textsubscript{2}-VASc scores were significantly higher in cases than controls (p<0.001).

The aORs of concomitant NSAIDs and SSRIs with NOACs af-
Use of NSAID or SSRI with NOAC Increases Bleeding

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

| 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)  | 1797 (72.9)       | <0.001  |
| CHA2DS2-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; SSRI, 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).
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 (n=1233) | Control (n=24660) | 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 (0.45–2.86)  | 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 (0.15–9.88)  | 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)  | 10.6 (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 bleedings1 (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 (1.11–2.83)  | 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, comedinations (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

| HAS-BLED score          | Case                  | Control               | Crude OR (95% CI) | Adjusted OR (95% CI)* |
|-------------------------|-----------------------|-----------------------|-------------------|-----------------------|
| 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)      |
| **p** for interaction=0.52 |                       |                       |                   |                       |
| 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 (55.2)           | Ref               | Ref                   |
| NSAIDs only             | 229 (40.2)            | 3468 (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)  | 1.86 (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 comediations 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. A recent study using a UK database reported no significant increase in concomitant NSAIDs use with NOAC. A higher prevalence of concomitant NSAIDs use with NOAC than previous studies (38.4% in present study; 5.2% in German study and 1.4% in UK population) 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.

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. SSRIs are known to inhibit platelet aggregation and also to directly decrease platelet adhesion to both collagen and fibrinogen. In addition, a potential increased OAC effect via inhibition of CYP450 by SSRIs has been reported.

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. To prevent upper GI bleeding, recent clinical guidelines 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. Lans, et al. 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, 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. Both NSAIDs and SSRIs showed significantly increased risks of urinary tract bleeding. Until now, there have been some case reports of NOAC-induced nephropathy. 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. 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. 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. 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 concomitant drugs, 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 CHA2DS2-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-
Use of NSAID or SSRI with NOAC Increases Bleeding

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REFERENCES

1. Lee SR, Choi EK, Han KD, Cha MJ, Oh S. Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA2DS2-VASc score in the entire Korean population. Int J Cardiol 2017;236:226-31.
2. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449-57.
3. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med 2000;160:41-6.
4. Chang SH, Chou II, Yeh YH, Chiou MJ, Wen MS, Kuo CT, et al. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. JAMA 2017;318:1250-9.
5. Zhang Y, Souverein PC, Gardarsdottir H, van den Ham HA, Maitland-van der Zee AH, de Boer A. Risk of major bleeding among users of direct oral anticoagulants combined with interacting drugs: a population-based nested case-control study. Br J Clin Pharmacol 2020;86:1150-64.
6. Jobksi K, Hoffmann F, Herget-Rosenthal S, Dörks M. Drug interactions with oral anticoagulants in German nursing home residents: comparison between vitamin K antagonists and non-vitamin K antagonist oral anticoagulants based on two nested case-control studies. Clin Res Cardiol 2020;109:465-75.
7. Schjerning Olsen AM, McGgettigan P, Gerds TA, Fosbol EL, Olsen JB, Sindet-Pedersen C, et al. Risk of gastrointestinal bleeding associated with oral anticoagulation and non-steroidal anti-inflammatory drugs in patients with atrial fibrillation: a nationwide study. Eur Heart J Cardiovasc Pharmacother 2019 Nov 19 [Epub]. Available at: https://doi.org/10.1093/ehjcvp/pvz069.
8. Kent AP, Brueckmann M, Fraessdorf M, Connolly SJ, Yusuf S, Eikelboom JW, et al. Consistent oral anticoagulant and nonsteroidal anti-inflammatory drug therapy in patients with atrial fibrillation. J Am Coll Cardiol 2018;72:255-67.
9. Renoux C, Vahey S, Dell’Aniello S, Boivin JF. Association of selective serotonin reuptake inhibitors with the risk for spontaneous intracranial hemorrhage. JAMA Neurol 2017;74:173-80.
10. Cheng YL, Hu HY, Lin XH, Luo JC, Peng YL, Hou MC, et al. Use of SSRI, but not SNRI, increased upper and lower gastrointestinal bleeding: a nationwide population-based cohort study in Taiwan. Medicine (Baltimore) 2015;94:e2022.
11. Shin JY, Park MJ, Lee SH, Choi SH, Kim MH, Choi NK, et al. Risk of intracranial haemorrhage in antidepressant users with concurrent use of non-steroidal anti-inflammatory drugs: nationwide propensity score matched study. BMJ 2015;351:h3517.
12. Bidxy AL, Vandenberg A, Bostwick JR. Clinical management of bleeding risk with antidepressants. Ann Pharmacother 2019;53:186-94.
13. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1390-93.
14. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:892-4.
15. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies. III. Design options. Am J Epidemiol 1992;135:1042-50.
16. Essebag V, Platt RW, Abrahamowicz M, Pilote L. Comparison of nested case-control and survival analysis methodologies for analysis of time-dependent exposure. BMC Med Res Methodol 2005;5:5.
17. Forbes HL, Polasek TM. Potential drug-drug interactions with direct oral anticoagulants in elderly hospitalized patients. Ther Adv Drug Saf 2017;8:319-28.
18. Jung SY, Jang EJ, Choi S, Im SG, Cho SK, et al. The effect of a nationwide real-time drug utilization review system on duplicated non-steroid anti-inflammatory drugs prescription in Korea. Arthritis Care Res (Hoboken) 2019 Aug 17 [Epub]. Available at: https://doi.org/10.1002acr.24054.
19. Quan H, Sundararajan V, Halton F, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130-9.
20. Olesen JB, Lip GY, Hansen PR, Lindhardsen J, Ashlehoft O, Anderson C, et al. Bleeding risk in ‘real world’ patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort. J Thromb Haemost 2011;9:1460-7.
21. Lanas Á, Carrera-Lasfuentes P, Arguedas Y, Garcia S, Bujanda L, Calvet X, et al. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. Clin Gastroenterol Hepatol 2015;13:906-12.
22. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. J Clin Pharmacol 1995;35:209-19.
23. de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. Drugs Aging 2011;28:345-67.
24. Bykov K, Schneeweiss S, Donneyong MM, Dong YH, Choudhry NK, Gagne JJ. Impact of an interaction between clopidogrel and selective serotonin reuptake inhibitors. Am J Cardiol 2017;119:651-7.
25. Andrade C, Sharma E. Serotonin reuptake inhibitors and risk of abnormal bleeding. Psychiatr Clin North Am 2016;39:413-26.
26. Maiden L, Thjodleifsson B, Seigal A, Bjarnason II, Scott D, Birgisson S, et al. Long-term effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective agents on the small bowel: a cross-sectional capsule enteroscopy study. Clin Gastroenterol Hepatol 2007;5:1040-5.
27. Boguta P, Juchnowicz D, Wróbel-Knybel P, Biela-Kędra A, Karakula-Juchnowicz H. Safety of concomitant treatment with non-vitamin K oral anticoagulants and SSRI/SNRI antidepressants. Curr Probl Psychiatry 2018;19:267-78.
28. Yuet WC, Derasari D, Sivoravong J, Mason D, Jann M. Selective serotonin reuptake inhibitor use and risk of gastrointestinal and intracranial bleeding. J Am Osteopath Assoc 2019;119:102-11.
29. Patel S, Hussain MA, Ajam F, Patel M, Nakrani M, Patel J, et al. Dabigatran-induced acute interstitial nephritis: an important complication of newer oral anticoagulation agents. J Clin Med Res 2018;10:791-4.
30. Monahan RC, Sutterp MM, Gabrëëls BATE. A case of rivaroxaban-associated acute tubulointerstitial nephritis. Neth J Med 2017;75:169-71.
31. Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsbøll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med 2010;170:1433-41.
32. Heidenreich PA, Solis P, Mark Estes NA 3rd, Fonarow GC, Jurgens CY, Marine JE, et al. 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Circ Cardiovasc Qual Outcomes 2016;9:443-88.