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Association Between Use of Non–Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation

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IMPORTANCE Non–vitamin K oral anticoagulants (NOACs) are commonly prescribed with other medications that share metabolic pathways that may increase major bleeding risk.

OBJECTIVE To assess the association between use of NOACs with and without concurrent medications and risk of major bleeding in patients with nonvalvular atrial fibrillation.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study using data from the Taiwan National Health Insurance database and including 91 330 patients with nonvalvular atrial fibrillation who received at least 1 NOAC prescription of dabigatran, rivaroxaban, or apixaban from January 1, 2012, through December 31, 2016, with final follow-up on December 31, 2016.

EXPOSURES NOAC with or without concurrent use of atorvastatin; digoxin; verapamil; diltiazem; amiodarone; fluconazole; ketoconazole, itraconazole, voriconazole, or posaconazole; cyclosporine; erythromycin or clarithromycin; dronedarone; rifampin; or phenytoin.

MAIN OUTCOMES AND MEASURES Major bleeding, defined as hospitalization or emergency department visit with a primary diagnosis of intracranial hemorrhage or gastrointestinal, urogenital, or other bleeding. Adjusted incidence rate differences between person-quarters (exposure time for each person during each quarter of the calendar year) of NOAC with or without concurrent medications were estimated using Poisson regression and inverse probability of treatment weighting using the propensity score.

RESULTS Among 91 330 patients with nonvalvular atrial fibrillation (mean age, 74.7 years [SD, 10.8]; men, 55.8%; NOAC exposure: dabigatran, 45 347 patients; rivaroxaban, 54 006 patients; and apixaban, 12 886 patients), 4770 major bleeding events occurred during 447 037 person-quarters with NOAC prescriptions. The most common medications co-prescribed with NOACs over all person-quarters were atorvastatin (27.6%), diltiazem (22.7%), digoxin (22.5%), and amiodarone (21.1%). Concurrent use of amiodarone, fluconazole, rifampin, and phenytoin with NOACs had a significant increase in adjusted incidence rates per 1000 person-years of major bleeding than NOACs alone: 38.09 for NOAC use alone vs 52.04 for amiodarone (difference, 13.94 [99% CI, 9.76-18.13]); 102.77 for NOAC use alone vs 241.92 for fluconazole (difference, 138.46 [99% CI, 80.96-195.97]); 65.66 for NOAC use alone vs 103.14 for rifampin (difference, 36.90 [99% CI, 1.59-72.22); and 56.07 for NOAC use alone vs 108.52 for phenytoin (difference, 52.31 [99% CI, 32.18-72.44]; $P < .01$ for all comparisons). Compared with NOAC use alone, the adjusted incidence rate for major bleeding was significantly lower for concurrent use of atorvastatin, digoxin, and erythromycin or clarithromycin and was not significantly different for concurrent use of verapamil; diltiazem; cyclosporine; ketoconazole, itraconazole, voriconazole, or posaconazole; and dronedarone.

CONCLUSIONS AND RELEVANCE Among patients taking NOACs for nonvalvular atrial fibrillation, concurrent use of amiodarone, fluconazole, rifampin, and phenytoin compared with the use of NOACs alone, was associated with increased risk of major bleeding. Physicians prescribing NOAC medications should consider the potential risks associated with concomitant use of other drugs.

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Atrial fibrillation is a common arrhythmia with an increasing prevalence and an association with thromboembolism and related adverse outcomes.[1] Oral anticoagulation has been proven to prevent ischemic strokes and prolong life for patients with atrial fibrillation.[2] Non-vitamin K oral anticoagulants (NOAC) are being used more frequently because of their ease of administration and comparative efficacy compared with warfarin in reducing thromboembolism and major bleeding.[3,4] However, for patients with atrial fibrillation, NOACs still pose a major bleeding risk,[5] which is particularly problematic when multiple morbidities, high-risk medications, polypharmacy, or drug-drug interactions are present.[6]

Two large clinical trials among patients with atrial fibrillation were conducted from 2006 through 2009 and approximately two-thirds of the participants (especially the elderly) took more than 5 drugs concurrently with a NOAC.[7,8] Polypharmacy among NOAC users may increase plasma levels and the risk of bleeding.[7] Current knowledge of drug-drug interactions associated with NOACs mainly comes from animal studies, case reports, and limited pharmacokinetic measurement.[9,10] Particular attention has been paid to medications (such as CYP3A4 inhibitors and P-glycoprotein competitors) that share common metabolic pathways with NOACs.[11,12] For example, ketoconazole and clarithromycin increase active NOAC levels in plasma and risk of bleeding.[10,13]

However, complex comedications and comorbidities hinder the quantification of bleeding risk associated with NOAC use in patients with atrial fibrillation.[6,14] Combining NOACs with other commonly used medications is generally avoided in clinical trials because the medications may alter NOAC levels in plasma and increase the risk of bleeding. To our knowledge, the influence of the concurrent use of CYP3A4 inhibitors or P-glycoprotein competitors on the magnitude of bleeding risk in NOAC users has not been quantified in the clinical setting. This study used a nationwide cohort of patients with nonvalvular atrial fibrillation to estimate the bleeding risk in NOAC users associated with the concurrent use of 12 commonly prescribed medications that share metabolic pathways with NOACs.

Key Points

Question What is the risk of major bleeding among patients with nonvalvular atrial fibrillation treated with non–vitamin K oral anticoagulants (NOACs) in combination with medications that share metabolic pathways?

Findings Among 91 330 NOAC users in Taiwan, the risk of major bleeding was significantly increased with concurrent use of amiodarone, fluconazole, rifampin, or phenytoin compared with NOAC use alone.

Meaning Physicians prescribing NOAC medications should consider the potential risks associated with concomitant use of other drugs.

Methods

Source of Data

This retrospective cohort study obtained ethical approval from the institutional review board of Taiwan Chang Gung Memorial Hospital and was conducted in full compliance with national ethical and regulatory guidelines. The institutional review board determined that patient consent was not required because all data were anonymized by the data holder, the Taiwan National Health Insurance Administration (NHIA). The Taiwan NHI system was established in 1995 as a single-payer insurance system co-funded by the government, employers, and beneficiaries. All citizens and foreigners living in Taiwan for more than 6 months are required by law to enroll in NHI. At the end of 2016, approximately 23 million beneficiaries were registered in NHI, which is equivalent to a coverage rate of 99.5%.

Novel medications, such as NOACs, are often approved and reimbursed by NHI, especially once clinical trials began providing evidence of efficacy and safety. Since 1995, the NHI database has recorded comprehensive registration information and claims data, which include patient characteristics, medical diagnoses, prescription details, examinations, operations, procedures, and fees incurred. The whole database is linked by the unique national personal identification, which was anonymized before its release for research use to prevent confidentiality leaks. The anonymized national personal identification remains consistent across the NHI database and between government-held data sets, allowing valid internal and external linkage.[15] The diagnoses and procedures were recorded using the *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) codes from 1997 through 2015 and the *International Classification of Diseases, 10th Revision, Clinical Modification* (*ICD-10-CM*) codes since 2016.

Study Population

We identified all patients (outpatients or inpatients) with 2 consecutive records of nonvalvular atrial fibrillation diagnosis (*ICD-9-CM* code 427.31 or *ICD-10-CM* code I48) [15] and at least 1 NOAC prescription (dabigatran, rivaroxaban, or apixaban) from January 1, 2012, through December 31, 2016. Patients with mitral stenosis or prosthetic valves were excluded because NOACs were not indicated in this population. Patients were followed up until death, deregistration, or the end of the study (December 31, 2016).

Follow-up Time and Person-Quarters

In this study, each calendar year was partitioned into 4 quarters for each patient and each year after the first prescription of a NOAC. The analytic unit was 1 person-quarter.[16] Person-quarters were used because medications for chronic illnesses were refilled with a maximum length of 3 months per the Taiwan NHI reimbursement policy. Medications and covariates were assessed for each person-quarter, which simplified the assessment of the complex prescription pattern of NOACs and multiple drugs. Person-quarters exposed to NOACs with

or without concurrent medications were identified. The major bleeding risks of person-quarters exposed to NOACs and 12 concurrent medications (atorvastatin; digoxin; verapamil; diltiazem; amiodarone; fluconazole; ketoconazole, itraconazole, voriconazole, or posaconazole; cyclosporine; erythromycin or clarithromycin; dronedarone; rifampin; and phenytoin) were compared with person-quarters exposed to NOAC alone. These medications were selected because they were P-glycoprotein competitors (digoxin, verapamil, diltiazem, amiodarone, and cyclosporine), CYP3A4 inhibitors (fluconazole and ketoconazole, itraconazole, voriconazole, or posaconazole), or both (atorvastatin, erythromycin or clarithromycin, dronedarone, rifampin, and phenytoin), which may have a potential drug-drug interaction with NOACs.[11,14,17-23]

Major Outcomes

The primary outcome was major bleeding, defined as a hospitalization or an emergency department visit with a primary diagnosis of intracranial hemorrhage or gastrointestinal, urogenital, or other bleeding, as previously described.[24] People with traumatic hemorrhage were excluded from analysis. Only 1 major bleeding event was included in each person-quarter. Secondary outcomes included site-specific bleeding. Details of case definitions for the primary outcome are listed in eTable 1 in the Supplement.

Covariates

Patient demographics, comorbidities, relevant medications, and health care utilization were identified as covariates.[15,25] These covariates were assessed for each person-quarter pertinent to the first date of the person-quarter. Patient demographics included age, sex, and socioeconomic factors (residence, income level, and occupation). The components of the Charlson comorbidity index (range, 0-37; a score of 5 points or more has a 1-y mortality rate of 85%[26]),[27] other comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, transient ischemic attack, dementia, chronic pulmonary disease, anemia, kidney diseases, and hepatic diseases), components of HAS-BLED (hypertension, abnormal kidney or liver function, stroke, bleeding history, and alcohol use), number of outpatient visits, proton pump inhibitors, aspirin, clopidogrel, ticlopidine, warfarin, nonsteroidal anti-inflammatory drugs, glucocorticoids, insulin, oral hypoglycemic agents, antihypertensives, and lipid-lowering agents were also assessed. The code lists of these covariates are shown in eTable 1 in the Supplement.

Models

Confounding by indication, which results from nonrandom treatment allocation for concurrent medications, was an essential consideration in the comparison of major bleeding risk among patients with NOAC use who were exposed vs unexposed to concurrent medications.[28,29] The inverse probability of treatment weighting using the propensity score was applied to account for this bias.[30] The propensity score was the probability that a patient was prescribed the concurrent medication during a person-quarter. For each person, a specific propensity score for a specific concurrent medication was calculated using logistic regression considering the aforementioned covariates pertinent to the first date of the person-quarter. Standardized differences were estimated to assess the balance of individual covariates before and after propensity score weighting. The balance of covariates was assessed using the absolute standardized mean difference. The negligible difference was defined as an absolute standardized mean difference less than 0.1. eTables 2A-L in the Supplement summarize the balance of covariates between users and nonusers of each specific concurrent medication.

Statistical Analysis

Poisson regression with a generalized estimating equations model to account for intra-individual correlation across person-quarters was used to calculate the adjusted incidence rate difference, incidence rate ratios, and 99% CIs with consideration of the inverse probability of treatment weighting using the propensity score. Person-quarters using NOAC alone were used as the reference category. Because 12 types of combinations were studied, the regression analysis was performed separately for each combination. In addition, a different definition of major bleeding—a hospitalization or emergency visits due to major bleeding recorded in the primary or secondary diagnosis—was applied as a sensitivity analysis.

Three additional analyses were conducted to ascertain the association of a NOAC plus concurrent medications and major bleeding: (1) The associations of a NOAC plus specific concurrent medications with bone fractures due to vehicle crashes (not related to the NOAC). (2) The association of the combination of losartan (a medication to replace NOAC in the model) plus concurrent medications with major bleeding (for details, see eTable 6C and 6D in the Supplement). (3) The association of a NOAC plus concurrent medication groups (ie, P-glycoprotein competitors group or CYP3A4 inhibitors group) with major bleeding.

The Bonferroni method was used to consider a type I error due to multiple comparisons. Three significance levels were used for hypothesis tests: .05, .01, and .005. The results were similar and the significance level of .01 was chosen to be reported in the main text. Estimates based on the alternative significance levels are reported in the eTables in the Supplement. Missing data were present among patients without a valid insurance status (estimated in <0.1% of NOAC users), and data associated with these patients were excluded. The entire analysis was performed using SAS (SAS Institute), version 9.4.

Results

Patient Characteristics

During 2012 to 2016, a total of 279 734 patients with nonvalvular atrial fibrillation were identified. Among them 91 330 patients received NOACs. The characteristics of the patients with nonvalvular atrial fibrillation at the first date of NOAC prescription are listed in **Table 1** and **Table 2**. The mean age was 74.7 years (SD, 10.8), and 55.8% of the studied population were men. The baseline average CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus,

Table 1. Characteristics and Comorbidities at Baseline Among Patients With Nonvalvular Atrial Fibrillation Taking a NOAC

Characteristic	NOAC Users (n = 91 330)
Age, mean (SD), y[a]	74.7 (10.8)
Men, No. (%)	50 937 (55.8)
Residence, No. (%)	
Urban	49 805 (54.53)
Suburban	28 667 (31.39)
Rural	12 424 (13.60)
Unknown	434 (0.48)
Occupation, No. (%)	
Dependents of the insured individuals	36 750 (40.24)
Civil servants, teachers, military personnel, and veterans	1303 (1.43)
Nonmanual workers and professionals	5065 (5.55)
Manual workers	28 240 (30.92)
Other	19 972 (21.87)
Income, 2017 US $	
Quintile 1	
Mean	41
Median (range)	42 (0-42)
No. of Patients (%)	27 893 (30.54)
Quintile 2	
Mean	555
Median (range)	667 (46-730)
No. of Patients (%)	5283 (5.78)
Quintile 3	
Mean	760
Median (range)	760 (760-760)
No. of Patients (%)	33 213 (36.37)
Quintile 4	
Mean	957
Median (range)	960 (800-1110)
No. of Patients (%)	6489 (7.11)
Quintile 5	
Mean	2002
Median (range)	1607 (1160-6067)
No. of Patients (%)	18 452 (20.20)
CHA_2DS_2-VASc score, mean (SD)[b]	3.9 (1.8)
HAS-BLED score, mean (SD)[c,d]	3.3 (1.3)
Charlson comorbidity index, mean (SD)[e]	2.4 (2.5)
No. of outpatient visits	
Mean	31
Median (range)	26 (0-226)
Comorbidities[c]	
Cardiovascular diseases, No. (%)	
Hypertension	65 754 (72.00)
Myocardial infarction	3900 (4.27)
Congestive heart failure	32 428 (35.51)
Percutaneous coronary intervention	2379 (2.60)
Coronary artery bypass surgery	86 (0.09)
Peripheral vascular disease	4011 (4.39)
Diseases of the nervous system, No. (%)	
Cerebrovascular disease	30 835 (33.76)
Ischemic stroke	22 862 (25.03)
Transient ischemic attack	4184 (4.58)
Hemiplegia and paraplegia	4161 (4.56)
Dementia	7343 (8.04)
Metabolic disease, No. (%)	
Diabetes mellitus	8163 (8.94)
Diabetes with complications	8168 (8.94)
Pulmonary disease, No. (%)	
Chronic pulmonary disease	18 370 (20.11)
Chronic obstructive pulmonary disease	15 613 (17.10)
Chronic kidney disease, No. (%)	
Not taking erythropoietin	90 067 (98.62)
Kidney impairment taking erythropoietin	1251 (1.37)
End-stage kidney disease	12 (0.01)
Gastrointestinal and hepatic disease, No. (%)	
Peptic ulcer disease	15 364 (16.82)
Mild liver disease[f]	9413 (10.31)
Moderate or severe liver disease[g]	343 (0.38)
Miscellaneous diseases, No. (%)	
Any malignancy, including leukemia and lymphoma	7944 (8.70)
Metastatic tumor	749 (0.82)
HIV infection	17 (0.02)
Major bleeding history	11 234 (12.30)
Anemia	4755 (5.21)
Rheumatic diseases	1057 (1.16)

Abbreviations: CHA_2DS_2-VASc, Congestive Heart Failure, Hypertension, Age ≥75 (Doubled), Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack (Doubled), Vascular Disease, Age 65-74, Female; NOAC, non–vitamin K oral anticoagulant; HAS-BLED, hypertension, abnormal kidney or liver function, stroke, bleeding history, and alcohol use.

[a] Measured at time of first appearance in sample.

[b] The CHA_2DS_2-VASc stroke score range is 0 to 9, males with a score more than 1 may consider anticoagulation.[31]

[c] Assessed during the 1 y before the first use of a NOAC.

[d] The HAS-BLED score range is 0 to 9 (a score >3 indicates higher bleeding risk).[32]

[e] The Charlson comorbidity index range is 0 to 37 (the 1-y mortality rate for a score of ≥5 is 85%).[26]

[f] Mild liver disease included viral hepatitis, acute and subacute necrosis of liver, and chronic liver cirrhosis.

[g] Moderate and severe liver disease included esophageal varices, hepatic coma, portal hypertension, and hepatorenal syndrome.

prior stroke or transient ischemic attack [doubled], vascular disease, age 65-74, female) stroke score (range 0-9, males with score >1 may consider anticoagulation)[31] was 3.9 (SD, 1.8) and the average HAS-BLED (hypertension, abnormal kidney or liver function, stroke, bleeding history, and alcohol use; range 0-9, a score >3 have higher bleeding risk)[32] score was 3.3 (SD, 1.3). More than one-third of the included patients were diagnosed with heart failure or cerebrovascular disease and a quarter with

Table 2. Medication Use During Follow-up Among Patients With Nonvalvular Atrial Fibrillation Taking a NOAC

Medication	NOAC Users, No. (%) (n = 91 330)
Aspirin	70 228 (76.89)
Rivaroxaban	54 006 (59.13)
Nonsteroid anti-inflammatory drugs	49 886 (54.62)
Atorvastatin	48 666 (53.29)
Dabigatran	45 347 (49.65)
Diltiazem	40 934 (44.82)
Clopidogrel	38 483 (42.14)
Amiodarone	37 737 (41.32)
Antihypertensive	34 075 (37.31)
Digoxin	33 181 (36.33)
Proton pump inhibitors	29 244 (32.02)
Glucocorticoids	26 382 (28.89)
Warfarin	25 427 (27.84)
Insulin	25 313 (27.72)
Lipid-lowering agents	18 985 (20.79)
Apixaban	12 886 (14.11)
Erythromycin or clarithromycin	12 878 (14.10)
Hypoglycemic agents	11 943 (13.08)
Ticlopidine	10 233 (11.20)
Verapamil	9246 (10.12)
Dronedarone	6033 (6.61)
Phenytoin	4816 (5.27)
Ticagrelor	3902 (4.27)
Fluconazole	2477 (2.71)
Other azoles[a]	1174 (1.29)
Rifampin	1151 (1.26)
Cyclosporine	567 (0.62)

Abbreviation: NOAC, non–vitamin K oral anticoagulant.

[a] Other azoles include ketoconazole, itraconazole, voriconazole, or posaconazole.

diabetes. There were 45 347 patients (49.7%) exposed to dabigatran, 54 006 patients (59.1%) to rivaroxaban, and 12 886 patients (14.1%) to apixaban during the follow-up period.

Bleeding Events

During follow-up, 4770 major bleeding events occurred during 447 037 person-quarters with NOAC prescriptions. The major bleeding events included 1177 intracranial and 3341 gastrointestinal bleedings and 182 events occurred in other sites. **Table 3** summarizes the incidence rate, adjusted incidence rate, and adjusted incidence rate difference for major bleeding among the 12 combinations of a NOAC and concurrent medications. The most common medications co-prescribed with NOACs over all person-quarters were atorvastatin (27.6%), diltiazem (22.7%), digoxin (22.5%), and amiodarone (21.1%). The combinations of a NOAC with amiodarone, fluconazole, rifampin, and phenytoin were associated with an increased risk of major bleeding. Compared with person-quarters of NOAC use alone (reference category), the adjusted incidence rate differences per 1000 person-years of major bleeding for a NOAC combined with other medications were 13.94 (99% CI, 9.76-18.13) with amiodarone, 138.46 (99% CI, 80.96-195.97) with fluconazole, 36.90 (99% CI, 1.59-72.22) with rifampin, and 52.31 (99% CI, 32.18-72.44) with phenytoin. The other combinations were not associated with any increase in bleeding risk. Atorvastatin, digoxin, and erythromycin or clarithromycin were associated with a reduced adjusted incidence rate difference of major bleeding (for data on the different significance levels, see eTable 3 in the Supplement).

Secondary Analysis

Separate analyses for dabigatran, rivaroxaban, and apixaban are summarized in **Table 4**. The patterns of bleeding risk associated with concurrent medications of dabigatran, rivaroxaban, or apixaban users were similar to the primary results. Concurrent medications of amiodarone, fluconazole, and phenytoin with a NOAC were associated with a higher major bleeding risk than NOAC use alone (for details, see eTables 4A-C in the Supplement).

Major bleeding events were classified anatomically into intracranial hemorrhage or bleeding in the gastrointestinal tract or other sites (including urogenital, pleural, or peritoneal bleeding). The adjusted incidence rate differences of major bleeding associated with the combinations of a NOAC and concurrent medications are listed in **Table 5**. The patterns of bleeding risks were similar in these bleeding sites.

Sensitivity and Additional Analyses

In a sensitivity analysis using alternative case definitions for major bleeding (hospitalization discharge or emergency visits recorded in the primary or secondary diagnoses), the adjusted incidence rate difference per 1000 person-years of major bleeding for a NOAC combined with other medications was 31.83 (99% CI, 26.40-37.26) with amiodarone, 265.25 (99% CI, 184.72-345.78) with fluconazole, 60.21 (99% CI, 4.79-115.63) with rifampin, and 80.10 (99% CI, 54.93-105.26) with phenytoin, showing an increase in bleeding rate ratios (for details, see eTable 6A and eTable 6B in the Supplement).

The first additional analysis was to evaluate the associations between the combination of losartan and 12 concurrent medications and major bleeding. None of the combinations was associated with an increased bleeding risk (for details, see eTable 6A and eTable 6C in the Supplement).

The second additional analysis examined whether the combination of a NOAC and 12 concurrent medications were associated with an unrelated adverse event, such as bone fractures. None of the combination was associated with an increased bone fracture risk (for details, see eTable 6A and eTable 6D in the Supplement).

In the third additional analysis, 12 concurrent medications were categorized into 2 metabolic pathway groups (P-glycoprotein competitors group (digoxin, verapamil, diltiazem, amiodarone, and cyclosporine) and both P-glycoprotein competitors and CYP3A4 inhibitors group (atorvastatin; fluconazole; ketoconazole, itraconazole, voriconazole, or posaconazole; erythromycin or clarithromycin; dronedarone; rifampin; and phenytoin). The combinations of NOAC with both groups were associated with a higher bleeding risk (for details, see eTable 7 in the Supplement).

Table 3. Major Bleeding Risk Among Patients Taking a NOAC for Nonvalvular Atrial Fibrillation With Concurrent Medications

Concurrent Medication	Person-Quarters With NOAC Use	No. of Bleeding Events	Crude Major Bleeding Incidence Rate (99% CI) per 1000 Person-Years	Adjusted Incidence Rate (99% CI) per 1000 Person-Years[a]	Adjusted Incidence Rate Difference (99% CI) per 1000 Person-Years[a]	Adjusted Rate Ratio (99% CI)[a]
Atorvastatin						
With	123 420	1056	34.22 (31.51 to 36.94)	34.57 (31.87 to 37.50)	−14.38 (−17.76 to −10.99)[b]	0.71 (0.64 to 0.78)[b]
Without[c]	323 617	3459	42.75 (40.88 to 44.63)	48.96 (46.48 to 51.57)		1 [Reference]
Digoxin						
With	100 513	1130	44.97 (41.52 to 48.42)	45.69 (42.23 to 49.43)	−4.46 (−8.45 to −0.47)[b]	0.91 (0.83 to 0.99)[b]
Without[c]	346 524	3413	39.40 (37.66 to 41.13)	50.14 (47.34 to 53.11)		1 [Reference]
Verapamil						
With	16 629	236	56.77 (47.25 to 66.29)	57.26 (48.30 to 67.88)	6.35 (−3.37 to 16.07)	1.12 (0.94 to 1.34)
Without[c]	430 408	4414	41.02 (39.43 to 42.61)	50.90 (48.54 to 53.38)		1 [Reference]
Diltiazem						
With	101 566	1300	51.20 (47.54 to 54.85)	51.91 (48.21 to 55.89)	−3.47 (−7.69 to 0.75)	0.94 (0.85 to 1.03)
Without[c]	345 471	3209	37.15 (35.47 to 38.84)	55.38 (51.90 to 59.10)		1 [Reference]
Amiodarone						
With	94 170	1207	51.27 (47.47 to 55.07)	52.04 (48.22 to 56.15)	13.94 (9.76 to 18.13)[b]	1.37 (1.25 to 1.50)[b]
Without[c]	352 867	3346	37.93 (36.24 to 39.62)	38.09 (36.19 to 40.10)		1 [Reference]
Fluconazole						
With	1938	117	241.24 (183.80 to 298.70)	241.92 (192.09 to 304.66)	138.46 (80.96 to 195.97)[b]	2.35 (1.80 to 3.07)[b]
Without[c]	445 099	4549	40.88 (39.32 to 42.44)	102.77 (89.76 to 117.66)		1 [Reference]
Other azoles[d]						
With	1276	13	40.75 (11.64 to 69.87)	40.83 (20.06 to 83.12)	−40.44 (−81.56 to 0.68)	0.50 (0.24 to 1.03)
Without[c]	445 761	4658	41.80 (40.22 to 43.38)	81.19 (72.27 to 91.22)		1 [Reference]
Cyclosporine						
With	744	10	53.76 (9.97 to 97.56)	53.80 (24.03 to 120.46)	−24.41 (−68.26 to 19.44)	0.69 (0.30 to 1.56)
Without[c]	446 293	4661	41.78 (40.20 to 43.35)	78.17 (67.72 to 90.22)		1 [Reference]
Erythromycin or clarithromycin						
With	14 251	211	59.22 (48.72 to 69.72)	59.38 (49.68 to 70.98)	−39.78 (−50.59 to −28.97)[b]	0.60 (0.48 to 0.75)[b]
Without[c]	432 786	4438	41.02 (39.43 to 42.60)	99.28 (87.21 to 113.01)		1 [Reference]
Dronedarone						
With	15 242	131	34.37 (26.64 to 42.11)	34.67 (27.53 to 43.66)	−4.20 (−12.11 to 3.72)	0.89 (0.71 to 1.13)
Without[c]	431 795	4531	41.97 (40.37 to 43.58)	38.83 (37.02 to 40.73)		1 [Reference]
Rifampin						
With	1405	36	102.56 (58.53 to 146.60)	103.14 (67.50 to 157.58)	36.90 (1.59 to 72.22)[b]	1.57 (1.02 to 2.41)[b]
Without[c]	445 632	4632	41.58 (40.00 to 43.15)	65.66 (61.33 to 70.30)		1 [Reference]
Phenytoin						
With	7158	191	106.70 (86.82 to 126.6)	108.52 (89.85 to 131.07)	52.31 (32.18 to 72.44)[b]	1.94 (1.59 to 2.36)[b]
Without[c]	439 879	4458	40.54 (38.97 to 42.10)	56.07 (52.93 to 59.40)		1 [Reference]

Abbreviation: NOAC, non–vitamin K oral anticoagulant.

[a] Adjusted by inverse probability of treatment weighting using the propensity score (sex, age, medical utilization, chronic kidney disease stage, anemia, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes, hemiplegia or paraplegia, any malignancy, moderate or severe liver disease, metastatic solid tumor, acquired immune deficiency syndrome, percutaneous coronary intervention, coronary artery bypass surgery, transient ischemic attack, hypertension, aspirin, clopidogrel, ticagrelor, ticlopidine, warfarin, glucocorticoids, insulin, lipid-lowering agents, hypoglycemic agents, antihypertensive, nonsteroid anti-inflammatory drugs, proton pump inhibitors, residence, income level, and occupation).

[b] $P < .01$.

[c] "Without" indicates NOAC alone.

[d] Other azoles include ketoconazole, itraconazole, voriconazole, or posaconazole.

Discussion

This nationwide population-based cohort study presents the following main findings. First, some specific medications advised to be avoided in NOAC users,[33] including diltiazem and amiodarone, were frequently prescribed to patients with nonvalvular atrial fibrillation in the clinical settings. Second, amiodarone, fluconazole, rifampin, and phenytoin were associated with a significantly increased risk of major bleeding, whereas some combinations not recommended by guidelines were not associated with major bleeding.

Table 4. Major Bleeding Risk Among Patients Taking Dabigatran, Rivaroxaban, or Apixaban for Nonvalvular Atrial Fibrillation With Concurrent Medications[a]

Concurrent Medication	Dabigatran		Rivaroxaban		Apixaban	
	Adjusted Incidence Rate Difference (99% CI)[b]	Adjusted Incidence Rate Ratio (99% CI)[b]	Adjusted Incidence Rate Difference (99% CI)[b]	Adjusted Incidence Rate Ratio (99% CI)[b]	Adjusted Incidence Rate Difference (99% CI)[b]	Adjusted Incidence Rate Ratio (99% CI)[b]
Atorvastatin	−16.11 (−20.98 to −11.24)[c]	0.66 (0.56 to 0.77)[c]	−12.35 (−17.32 to −7.38)[c]	0.76 (0.66 to 0.87)[c]	−17.50 (−29.59 to −5.41)[c]	0.69 (0.51 to 0.92)[c]
Digoxin	−5.50 (−11.14 to 0.15)	0.89 (0.76 to 1.04)	−2.06 (−7.95 to 3.82)	0.96 (0.83 to 1.11)	−6.28 (−22.32 to 9.75)	0.89 (0.65 to 1.23)
Verapamil	1.53 (−12.62 to 15.68)	1.03 (0.76 to 1.38)	9.08 (−4.71 to 22.87)	1.17 (0.90 to 1.52)	−2.74 (−36.10 to 30.62)	0.95 (0.51 to 1.77)
Diltiazem	−8.13 (−16.34 to 0.08)	0.85 (0.72 to 1.01)	1.70 (−4.46 to 7.86)	1.03 (0.89 to 1.19)	3.24 (−12.58 to 19.05)	1.05 (0.79 to 1.40)
Amiodarone	13.08 (6.86 to 19.30)[c]	1.36 (1.17 to 1.59)[c]	15.41 (9.43 to 21.39)[c]	1.38 (1.21 to 1.58)[c]	12.51 (−1.43 to 26.44)	1.30 (0.98 to 1.72)
Fluconazole	148.55 (48.28 to 248.82)[c]	2.26 (1.44 to 3.55)[c]	118.10 (49.01 to 187.20)[c]	2.25 (1.54 to 3.30)[c]	226.00 (18.73 to 433.27)[c]	3.36 (1.69 to 6.68)[c]
Other azoles[d]	−51.36 (−114.56 to 11.84)	0.48 (0.18 to 1.33)	−24.75 (−74.41 to 24.90)	0.69 (0.25 to 1.89)	NA	NA
Cyclosporine	−50.72 (−101.68 to 0.23)	0.40 (0.08 to 2.06)	−32.05 (−90.02 to 25.91)	0.58 (0.14 to 2.40)	196.68 (53.93 to 339.43)[c]	4.99 (1.43 to 17.36)[c]
Erythromycin or clarithromycin	−66.04 (−81.32 to −50.76)[c]	0.43 (0.29 to 0.64)[c]	−18.19 (−36.39 to 0.41)	0.79 (0.58 to 1.06)	−65.47 (−98.61 to −32.33)[c]	0.41 (0.19 to 0.88)[c]
Dronedarone	−4.96 (−20.56 to 10.63)	0.89 (0.54 to 1.45)	−3.02 (−13.02 to 6.98)	0.92 (0.68 to 1.24)	−12.74 (−32.89 to 7.40)	0.68 (0.33 to 1.41)
Rifampin	48.43 (−20.37 to 117.22)	1.76 (0.91 to 3.42)	37.51 (−24.73 to 99.75)	1.59 (0.82 to 3.09)	−33.64 (−116.35 to 49.07)	0.49 (0.04 to 6.53)
Phenytoin	54.09 (26.20 to 81.98)[c]	2.09 (1.53 to 2.85)[c]	51.84 (21.93 to 81.76)[c]	1.85 (1.36 to 2.51)[c]	54.57 (−27.5 to 136.65)	1.80 (0.90 to 3.60)

Abbreviation: NA, not applicable.

[a] For more details, see eTable 4 in the Supplement.

[b] Incidence rate difference indicates the difference in incidence rates between person-quarters exposed to a non–vitamin K oral anticoagulant with or without concurrent medication. Adjusted by inverse probability of treatment weighting using the propensity score (sex, age, medical utilization, chronic kidney disease stage, anemia, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes, hemiplegia or paraplegia, any malignancy, moderate or severe liver disease, metastatic solid tumor, acquired immune deficiency syndrome, percutaneous coronary intervention, coronary artery bypass surgery, transient ischemic attack, hypertension, aspirin, clopidogrel, ticagrelor, ticlopidine, warfarin, glucocorticoids, insulin, lipid-lowering agents, hypoglycemic agents, antihypertensive, nonsteroid anti-inflammatory drugs, proton pump inhibitors, residence, income level, and occupation).

[c] *P* value was less than .01.

[d] Other azoles include ketoconazole, itraconazole, voriconazole, or posaconazole.

Although the 12 concurrent medications evaluated in this study are not recommended by the updated guidelines,[33] they are often required for NOAC users in many clinical scenarios. Digoxin, diltiazem, amiodarone, and atorvastatin were used in more than 20% of NOAC-exposed person-quarters. This is in line with the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) and the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trials, which reported that approximately 30% and 10% of NOAC users were prescribed digoxin or amiodarone, respectively.[34-36] On the other hand, prescription of cyclosporine and antifungal azoles to NOAC users was rarely found.

There was a difference between the data from this study and clinical trials. In most trials, the concurrent medication status was reported as part of the baseline characteristics and percentage numbers of total patients enrolled. The estimates in this study, however, were the person-quarter exposed to a NOAC and concurrent medications, which reflected the dynamic and complex prescription pattern of concurrent medications in NOAC users in a more precise manner. To our knowledge, the prevalence of rare combinations, such as antifungal azoles or cyclosporine, with a NOAC has not been reported in the literature. These infrequent combinations, however, do not necessarily carry a lower risk of major bleeding.

Amiodarone plus a NOAC was associated with significantly more major bleeding events in all primary and secondary analyses. During observation periods, the combination of a NOAC and amiodarone use was associated with an adjusted incidence rate difference for major bleeding of 13.94 events per 1000 person-years, which probably exceeds any benefit that such a combination could deliver. This is, to our knowledge, a novel observation because (1) the combination is frequent in clinical settings, and (2) a subanalysis of the ARISTOTLE trial showed no difference in major bleeding between apixaban users with and without amiodarone use.[36] The highest bleeding risk was found in the combination of fluconazole and a NOAC, with an adjusted incidence rate difference of 138.46 events per 1000 person-years. Therefore, fluconazole should be avoided in NOAC users.

Paradoxically, several combinations were associated with lower bleeding risk. Atorvastatin was reported to reduce all stoke and not to increase intracranial hemorrhage.[37-39] The lower bleeding rate associated with atorvastatin found in this study might be partially related to the prevention of hemorrhagic transformation after ischemic stroke. Statins had been

Table 5. Site-Specific Major Bleeding Risk Among Patients Taking Non–Vitamin K Oral Anticoagulants for Nonvalvular Atrial Fibrillation With Concurrent Medications[a]

	Intracranial Hemorrhage		Gastrointestinal Bleeding		Bleeding in Other Sites	
Concurrent Medication	Adjusted Incidence Rate Difference (99% CI)[b]	Adjusted Incidence Rate Ratio (99% CI)[b]	Adjusted Incidence Rate Difference (99% CI)[b]	Adjusted Incidence Rate Ratio (99% CI)[b]	Adjusted Incidence Rate Difference (99% CI)[b]	Adjusted Incidence Rate Ratio (99% CI)[b]
Atorvastatin	−5.37 (−7.25 to −3.49)[c]	0.60 (0.49 to 0.73)[c]	−8.83 (−11.89 to −5.77)[c]	0.74 (0.66 to 0.83)[c]	−0.28 (−1.02 to 0.45)	0.85 (0.54 to 1.35)
Digoxin	0.30 (−1.74 to 2.34)	1.02 (0.85 to 1.23)	−4.11 (−7.57 to −0.64)[c]	0.89 (0.79 to 0.99)[c]	−0.52 (−1.31 to 0.26)	0.73 (0.43 to 1.21)
Verapamil	0.42 (−4.23 to 5.08)	1.03 (0.72 to 1.47)	4.90 (−2.87 to 12.67)	1.14 (0.92 to 1.40)	1.00 (−0.79 to 2.79)	1.53 (0.70 to 3.35)
Diltiazem	1.24 (−0.92 to 3.41)	1.09 (0.91 to 1.31)	−4.18 (−7.81 to 0.01)	0.90 (0.80 to 1.01)	−0.49 (−1.31 to 0.33)	0.77 (0.46 to 1.28)
Amiodarone	8.14 (4.29 to 11.98)[c]	1.97 (1.67 to 2.34)[c]	5.64 (0.13 to 11.42)[c]	1.20 (1.07 to 1.34)[c]	0.21 (−1.17 to 1.60)	1.15 (0.73 to 1.82)
Fluconazole	44.16 (26.77 to 61.55)[c]	3.03 (1.82 to 5.07)[c]	93.65 (60.50 to 126.79)[c]	2.18 (1.59 to 3.00)[c]	1.91 (−3.61 to 7.43)	1.86 (0.28 to 12.27)
Other azoles[d]	−14.42 (−35.18 to 6.33)	0.30 (0.05 to 1.89)	−23.84 (−58.69 to 11.02)	0.59 (0.27 to 1.30)	NA	NA
Cyclosporine	−8.02 (−33.90 to 17.87)	0.57 (0.09 to 3.57)	−19.51 (−64.69 to 25.66)	0.66 (0.25 to 1.76)	2.87 (−6.61 to 12.35)	2.15 (0.16 to 29.06)
Erythromycin or clarithromycin	−12.65 (−19.41 to −5.89)[c]	0.48 (0.30 to 0.76)[c]	−29.65 (−41.41 to −17.88)[c]	0.59 (0.46 to 0.77)[c]	1.41 (−1.04 to 3.86)	1.46 (0.57 to 3.77)
Dronedarone	−2.60 (−6.70 to 1.50)	0.73 (0.43 to 1.24)	−2.91 (−10.01 to 4.20)	0.89 (0.68 to 1.18)	1.03 (−0.68 to 2.74)	1.65 (0.71 to 3.86)
Rifampin	17.02 (0.51 to 33.53)[c]	0.48 (0.30 to 0.76)[c]	15.56 (−15.24 to 46.35)	1.32 (0.77 to 2.27)	4.04 (−1.60 to 9.67)	3.43 (0.54 to 21.65)
Phenytoin	50.38 (42.94 to 57.81)[c]	4.62 (3.52 to 6.05)[c]	0.92 (−11.42 to 13.26)	1.02 (0.75 to 1.38)	1.90 (−0.87 to 4.67)	1.94 (0.70 to 5.37)

Abbreviation: NA, not applicable.

[a] For more details, see eTable 5 in the Supplement.

[b] Incidence rate difference indicates the difference in incidence rates between person-quarters exposed to a non–vitamin K oral anticoagulant with or without concurrent medication. Adjusted by inverse probability of treatment weighting using the propensity score (sex, age, medical utilization, chronic kidney disease stage, anemia, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes, hemiplegia or paraplegia, any malignancy, moderate or severe liver disease, metastatic solid tumor, acquired immune deficiency syndrome, percutaneous coronary intervention, coronary artery bypass surgery, transient ischemic attack, hypertension, aspirin, clopidogrel, ticagrelor, ticlopidine, warfarin, glucocorticoids, insulin, lipid-lowering agents, hypoglycemic agents, antihypertensive, nonsteroid anti-inflammatory drugs, proton pump inhibitors, residence, income level, and occupation).

[c] *P* value was less than .01.

[d] Other azoles include ketoconazole, itraconazole, voriconazole, or posaconazole.

suggested to decrease gastrointestinal bleeding rates in patients with acute coronary syndromes.[40] Considering the cardiovascular benefit of atorvastatin and a lack of increased bleeding risk, clinicians should not avoid using atorvastatin with a NOAC in patients with nonvalvular atrial fibrillation. The crude bleeding rate of erythromycin or clarithromycin combined with a NOAC was higher than NOAC use alone, but adjusted rates were higher in the NOAC use alone group. The most plausible explanation was that clarithromycin was an integral part of antibiotic treatment for *Helicobacter pylori* infection.[41] The reduction of peptic ulcer bleeding risk by anti-*Helicobacter* treatment seems to outweigh the potential bleeding risk brought by an increase in plasma concentration of the NOAC as a result of the concurrent use of macrolide. The lower bleeding rate associated with digoxin was marginal. Considering the relatively unchanged plasma levels found in a pharmacokinetic study of dabigatran,[20] digoxin plus NOACs might be considered a safe combination.

Many combinations were found to increase NOAC levels in plasma in the pharmacokinetic studies,[11,18-20,22] but were not associated with increased risk of bleeding in this cohort study. For example, there were discrepancies between pharmacokinetic interaction and clinically relevant bleeding risk observed in atorvastatin, digoxin, verapamil, cyclosporine, or clarithromycin or erythromycin. On the other hand, shared metabolic pathways might explain the high bleeding risk of NOACs plus fluconazole or amiodarone. The most plausible reason for this discrepancy may be that higher plasma levels of NOAC did not necessarily result in more bleeding, which was also related to the comorbidity and the main drug benefits of the concurrent medications. Another reason might be that the limited pharmacokinetic data of NOAC use was mostly collected from healthy volunteers who have different pharmacokinetic profiles from NOAC users, who tend to be older, with more comorbidity and polypharmacy.

This is the first, to our knowledge, nationwide population-based cohort study to quantify the major bleeding risk associated with drug-drug interaction with NOACs. The person-quarter model with inverse probability of treatment weighting using the propensity score helped to overcome confounding by indication bias and the complex prescription pattern in clinical setting. The design focused on a short-term risk of adverse events and addressed the unstable complex prescribing behavior. Complex prescription decision making for the use of concurrent medications (based on changes in patients' clinical conditions) was considered in the model with the probability of treatment weighting using the propensity score in each person-quarter. The observed association between the use

of NOACs concurrently with specific medications and a risk of major bleeding was unlikely related to unmeasured bleeding characteristics.

Several major potential applications could be derived from this study. First, prompt or even real-time postmarket monitoring is possible. In most standard clinical trials, it is impractical to measure the risk of a specific major adverse event related to any drug combination. With the design applied in this study, severe adverse effects of new combinations of medications might be detected earlier. Second, systemic and automatic monitoring of the safety profiles of new drugs with automatic data processing is possible. It is feasible to combine a pharmacology database that contains potential drug-drug interactions with a clinical database and the methodology used in this study to quantify the risk of potential adverse events.

Limitations

This study had several limitations. First, because edoxaban was introduced in Taiwan after 2016, not all NOACs were studied. Although similar interactions and patterns were found in all other 3 NOACs, these observations may not apply to edoxaban. Second, kidney and liver function data were not available in the NHI database and these factors may interfere with drug-drug interaction, bleeding risk, and medication dosing. However, some proxy indicators (such as erythropoietin for severe kidney disease and diagnosis of liver diseases) were added in the model to represent the severity of kidney or hepatic diseases. Third, bleeding risk and anticoagulant treatment in the Asian population have been recognized to be different from the Western population.[42] Therefore, the external generalizability of these results, particularly to Western population may be limited. Fourth, dosages of NOACs and the studied medications were not considered in the model because it would have complicated the complex model further.

Conclusions

Among patients taking NOACs for nonvalvular atrial fibrillation, concurrent use of amiodarone, fluconazole, rifampin, and phenytoin compared with the use of NOACs alone, was associated with increased risk of major bleeding. Physicians prescribing NOAC medications should consider the potential risks associated with concomitant use of other drugs.

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