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ORIGINAL RESEARCH

Concomitant Drug Interactions With Non–Vitamin K Oral Anticoagulants Are Associated With Bleeding and Mortality Risk in Patients With Nonvalvular Atrial Fibrillation

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BACKGROUND: Non–vitamin K oral anticoagulants prevent stroke and systemic embolism in patients with nonvalvular atrial fibrillation. However, potential drug interactions with concomitant medications may compromise their efficacy and escalate the risk of adverse effects.

METHODS AND RESULTS: We conducted a territory-wide retrospective cohort study in Hong Kong, focusing on nonvalvular atrial fibrillation prescribed non–vitamin K oral anticoagulants. The objective was to investigate the associated risk of gastrointestinal bleeding, intracranial hemorrhage, hospitalization for major bleeding, and all-cause mortality in relation to various concomitant medications. Our analysis included 22 568 patients with nonvalvular atrial fibrillation (aged 75.7 ± 10.8 years; 51.2% men) taking non–vitamin K oral anticoagulants from January 1, 2017, to December 31, 2020, totaling 40 317 patient-years. It was found that amiodarone (hazard ratio [HR], 1.53), digoxin (HR, 1.30), diltiazem (HR, 1.18), clarithromycin (HR, 4.98), and fluconazole (HR, 2.38) were associated with increased gastrointestinal bleeding, whereas amiodarone (HR, 2.20) and digoxin (HR, 1.61) were associated with increased intracranial hemorrhage. Furthermore, amiodarone (HR, 1.64), digoxin (HR, 1.35), clarithromycin (HR, 4.18), and fluconazole (HR, 2.40) were associated with increased hospitalization for major bleeding. Additionally, amiodarone (HR, 2.65), digoxin (HR, 1.85), diltiazem (HR, 1.44), verapamil (HR, 1.80), antidepressants (HR, 1.31), and fluconazole (HR, 3.27) were associated with increased all-cause mortality. Conversely, dronedarone (HR, 0.56) and atorvastatin (HR, 0.86) were associated with a significant reduction in all-cause mortality.

CONCLUSIONS: For patients with nonvalvular atrial fibrillation taking non–vitamin K oral anticoagulants, several concurrent medications were associated with increased risks of intracranial hemorrhage, major bleeding hospitalizations, and overall mortality.

Key Words: bleeding ■ drug interaction ■ mortality ■ nonvalvular atrial fibrillation ■ non–vitamin K oral anticoagulant

Atrial fibrillation (AF) is the most common sustained arrhythmia and increases the risk of ischemic stroke.[1,2] Anticoagulation therapy with vitamin K antagonist, warfarin, in patients with nonvalvular AF (NVAF) has been shown to reduce the risk of ischemic stroke.[3,4] Nevertheless, its clinical efficacy

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CLINICAL PERSPECTIVE

What Is New?

- In a territory-wide retrospective cohort study involving patients who took non–vitamin K oral anticoagulant for nonvalvular atrial fibrillation, amiodarone, digoxin, diltiazem, clarithromycin, and fluconazole were associated with increased gastrointestinal bleeding; amiodarone and digoxin were associated with increased intracranial hemorrhage; amiodarone, digoxin, clarithromycin, and fluconazole were associated with increased hospitalization for major bleeding; and amiodarone, digoxin, diltiazem, verapamil, antidepressants, and fluconazole were associated with increased all-cause mortality.
- Conversely, dronedarone and atorvastatin were associated with a reduction in all-cause mortality.

What Are the Clinical Implications?

- It is crucial for clinicians to be aware of potential drug-drug interactions when prescribing non–vitamin K oral anticoagulant, particularly those mediated through cytochrome P450 and P-glycoprotein.

Nonstandard Abbreviations and Acronyms

CYP	cytochrome P450
NOAC	non–vitamin K oral anticoagulant
NVAF	nonvalvular atrial fibrillation

and safety depend on achieving a sustained time in therapeutic range.[5] In a real-world setting, achieving a high percentage of time in the therapeutic range for warfarin is a challenge in many patients because warfarin interacts with a multitude of medications and is sensitive to dietary intake of vitamin K.[6] More recently, non–vitamin K oral anticoagulants (NOACs), such as apixaban,[7] dabigatran,[8] edoxaban,[9] and rivaroxaban,[10] have been increasingly prescribed as a preferred anticoagulant in NVAF as they have been shown to reduce stroke and systemic embolism by 19%, all-cause mortality by 10%, and intracranial hemorrhage by 52% compared with warfarin.[11] In addition, long-term monitoring of drug level is not required, and there are fewer interactions with other medications.

Despite these advantages, the plasma level of NOACs and thus their anticoagulation effects can be affected by the concomitant use of potent cytochrome P450 (CYP) and P-glycoprotein inhibitors.[12] Retrospective studies from Canada demonstrated that >4% of patients prescribed an NOAC also received medications that were classified as either contraindicated or cautious use, and said use was associated with increased mortality.[13] Moreover, recent retrospective cohort studies from a Taiwan insurance database revealed an increased risk of major bleeding when an NOAC was prescribed concomitantly with amiodarone, fluconazole, rifampin, and phenytoin.[14] Similarly, observational study from the United States and Belgium demonstrated higher bleeding risk when diltiazem was used in conjunction with NOACs.[15,16] It remains unclear whether the increased mortality was related to the presence of coexistent underlying diseases that required these medications or attributable to fatal bleeding, such as intracranial hemorrhage consequent to a drug interaction. In this study, we performed a territory-wide retrospective cohort study using the comprehensive electronic health record system in Hong Kong of patients with NVAF who were prescribed an NOAC to investigate the potential risk of gastrointestinal bleeding, intracranial hemorrhage, hospitalization for major bleeding, and all-cause mortality attributable to interaction with different concomitant medications.

METHODS

The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (UW 12-177). The requirement of informed consent from patients was waived as the study involved only retrospective analysis of anonymized data from the hospital registry. The article follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[17]

Data Availability Statement

Anonymized data are available from the corresponding author on reasonable requests from the date of publication for 3 years.

Study Participants

Adult patients, aged ≥18 years, diagnosed with NVAF in the Accident and Emergency Department or Specialist Out-patient Clinic in Hong Kong, and first commenced on apixaban, dabigatran, edoxaban, or rivaroxaban for stroke prevention between January 1, 2017, and December 31, 2020, were included in this study. Patients were excluded if they had valvular heart disease or died at first AF occurrence. Valvular heart diseases include aortic, mitral, pulmonary, and tricuspid valve replacement, as well as those with mitral stenosis.

Data Source and Study Procedure

Patients were identified using the Clinical Data Analysis and Reporting System of the Hospital Authority in Hong

Kong. The Hospital Authority is an institution that manages all public hospitals and outpatient clinics in Hong Kong and provides health care services to >90% of the citizens. Clinical Data Analysis and Reporting System is an internationally recognized electronic health record database with large population coverage, comprehensive clinical data, and excellent data quality, and has been used to conduct high-quality pharmacoepidemiologic studies.[18] Demographic data, including age and date of birth, and cardiovascular comorbidities, including hypertension, hyperlipidemia, diabetes, ischemic heart disease, heart failure, and stroke, were recorded. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. CHA_2DS_2-VASc score is a composite score incorporating congestive heart failure, age, diabetes, stroke or systemic embolism, vascular disease, and sex category.[19] The occurrence of adverse clinical outcomes, including intracranial hemorrhage, gastrointestinal bleeding, hospitalization for major bleeding attributable to intracranial hemorrhage and/or gastrointestinal bleeding, and all-cause mortality, was extracted. Gastrointestinal bleeding was evaluated because previous randomized controlled trials demonstrated NOAC patients are at high risk of developing the adverse event than those taking warfarin.[11] Gastrointestinal bleeding in the esophagus, stomach, duodenum, and small and large bowels was included in this study, with details on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), codes used listed in Table S1.

Concomitant medications with possible drug-drug interaction with NOACs listed in the 2021 European Heart Rhythm Association Practical Guide on the Use of Non–Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation were extracted from the Clinical Data Analysis and Reporting System using the British National Formulary classification, as follows: antiarrhythmic (amiodarone, digoxin, diltiazem, dronedarone, and verapamil), antidepressant (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, desvenlafaxine, duloxetine, venlafaxine, trazodone, amitriptyline, clomipramine, imipramine, dosulepin, nortriptyline, and bupropion), antimicrobial (clarithromycin, erythromycin, fluconazole, itraconazole, voriconazole, and posaconazole), and atorvastatin.[12] Flecainide and β-blockers, which are not expected to have drug-drug interaction with NOAC, were included in the analysis as control groups.

Statistical Analysis

Continuous variables were tested for normal distribution using skewness statistics. Baseline data are reported as mean and SD for continuous data and as number and percentage for categorical data. Comparison between groups were performed using Student *t*-test for continuous variables, and χ^2 test for categorical variables.

Drug treatment period was defined using start and end date of NOAC. Crude hazard ratio (HR) was calculated using Cox proportional hazard model with R package "survival" version 3.5-5. The proportional hazards assumption was assessed through examination of Schoenfeld residuals. Adjusted HR was calculated after adjustment for age, sex, and presence of hypertension, diabetes, hyperlipidemia, ischemic heart disease, heart failure, stroke, and CHA_2DS_2-VASc score. In addition to baseline characteristics with significant differences, adjustment for use of antiplatelets and NSAID was included as they may potentially increase gastrointestinal and overall bleeding risks. $P<0.05$ was considered statistically and denoted by asterisk (*).

RESULTS

During the study period, 22 568 patients with NVAF and follow-up at public hospitals and outpatient clinics managed by the Hospital Authority in Hong Kong were prescribed 1 of the 4 analyzed NOACs (Figure 1). Table 1 summarizes their baseline characteristics. Their mean±SD age was 75.7±10.8 years, and 51.2% were men. Among the finally analyzed patients, 6602 (29.3%) had hypertension, 3105 (13.8%) had hyperlipidemia, 2825 (12.5%) had diabetes, 2321 (10.3%) had ischemic heart disease, 2037 (9.02%) had heart failure, and 2383 (10.6%) had a history of stroke. The mean±SD CHA_2DS_2-VASc score was 2.70±1.60. Apixaban, dabigatran, edoxaban, and rivaroxaban were prescribed to 11 601 (51.4%), 6963 (30.9%), 774 (3.42%), and 3230 (14.3%) patients, respectively.

Concomitant Medication Prescription

Table 2 summarizes concomitant use of an NOAC with different interacting medications. The most commonly prescribed medications with possible drug-drug interaction with an NOAC were atorvastatin (26.4%), digoxin (19.0%), diltiazem (14.4%), and amiodarone (13.9%). The remaining medications were concomitantly prescribed to <10% of patients, including dronedarone (2.00%), verapamil (0.80%), clarithromycin (1.25%), erythromycin (0.11%), fluconazole (0.36%), other azoles (0.49%), and antidepressants (7.60%). β-Blockers (37.3%) and flecainide (0.85%) were included as control, with baseline characteristics summarized in Table S2. Overall, β-blocker users were younger, had higher rate of concomitant cardiovascular risk factors and diseases, and had higher CHA_2DS_2-VASc score. Flecainide users were more likely younger, had better renal function, had less heart failure, and had lower CHA_2DS_2-VASc score. Characteristics of patients taking clarithromycin

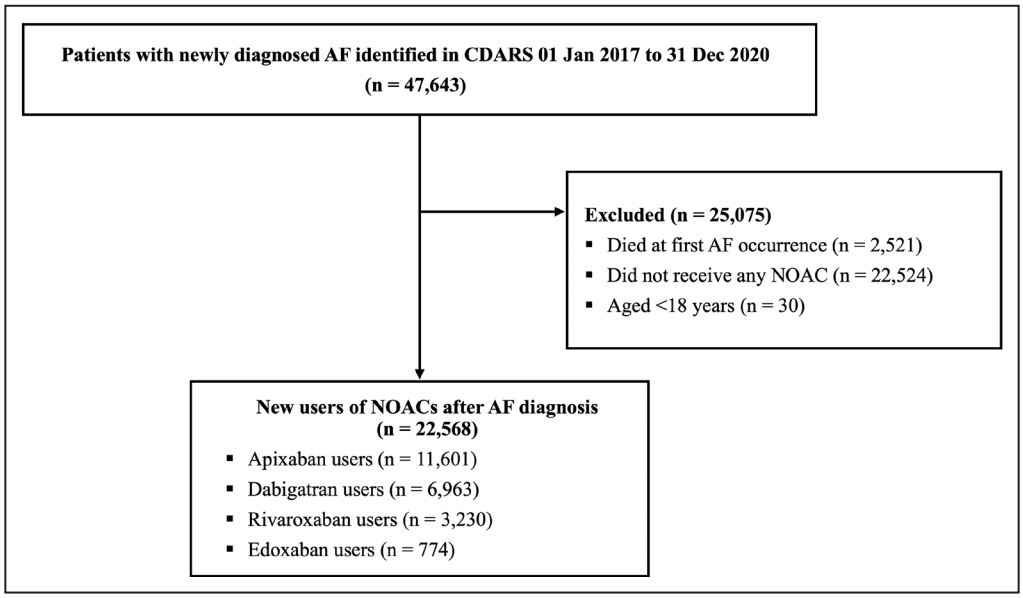

Figure 1. Flowchart of cohort selection.
AF indicates atrial fibrillation; CDARS, Clinical Data Analysis and Reporting System; and NOAC, non–vitamin K oral anticoagulant.

and fluconazole were similarly summarized in Table S2. Patients who took clarithromycin were more likely to be men and had higher proportion of diabetes. Patients who were prescribed fluconazole had higher proportion of heart failure and worse renal function (Table S2).

Adverse Clinical Outcomes

The analyzed patients were followed up for a total of 40 317 patient-years, including 18 735 patient-years for apixaban, 13 936 for dabigatran, 1092 for edoxaban, and 6554 for rivaroxaban. Table 3 summarizes the proportion of patients who experienced the prespecified adverse events. Adjusted HR was calculated after adjusting for sex, age, estimated glomerular filtration rate, hypertension, diabetes, hyperlipidemia, ischemic heart disease, heart failure, stroke, CHA_2DS_2-VASc score, antiplatelet, and NSAIDs.

Gastrointestinal Bleeding

Overall, 1113 patients (4.93%) had gastrointestinal bleeding during the follow-up period. Adjustment for confounding factors, including NSAIDs, which increase gastrointestinal bleeding risk, was performed. Amiodarone (adjusted HR, 1.53 [95% CI, 1.31–1.78];

Table 1. Baseline Characteristics

Characteristic	All patients	Without potential drug-drug interaction	With potential drug-drug interaction	*P* value
No. of patients	22 568	6361	16 207	
Age, mean±SD, y	75.7±10.8	77.4±10.2	75.0±10.9	<0.01*
Male sex, n (%)	11 554 (51.2)	33 371 (53.0)	8183 (50.5)	<0.01*
Hypertension, n (%)	6602 (29.3)	1223 (19.2)	5379 (33.2)	<0.01*
Hyperlipidemia, n (%)	3105 (13.8)	580 (9.12)	2525 (15.6)	<0.01*
Diabetes, n (%)	2825 (12.5)	517 (8.13)	2308 (14.2)	<0.01*
Ischemic heart disease, n (%)	2321 (10.3)	292 (4.59)	2029 (12.5)	<0.01*
Heart failure, n (%)	2037 (9.02)	277 (4.35)	1760 (10.9)	<0.01*
Stroke, n (%)	2383 (10.6)	481 (7.56)	1902 (11.7)	<0.01*
eGFR, mean±SD, mL/min per 1.73 m^2†	66.2±19.9	66.1±19.7	66.3±19.9	0.52
CHA_2DS_2-VASc, mean±SD‡	2.70±1.60	2.50±1.40	2.80±1.70	<0.01*

eGFR indicates estimated glomerular filtration rate.
*Indicates *P*<0.05.
†eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.
‡CHA_2DS_2-VASc score is a composite score incorporating congestive heart failure, age, diabetes, stroke or systemic embolism, vascular disease, and sex category.

Table 2. Concomitant Medications

Medications	No. (%) of patients
Antiarrhythmic drugs	
Amiodarone	3143 (13.9)
β-Blockers*	8413 (37.3)
Digoxin	4290 (19.0)
Diltiazem	3247 (14.4)
Dronedarone	448 (2.00)
Flecainide*	191 (0.85)
Verapamil	180 (0.80)
Antimicrobial agents	
Clarithromycin	282 (1.25)
Erythromycin	24 (0.11)
Fluconazole	82 (0.36)
Other azoles	110 (0.49)
Antidepressants	1716 (7.60)
Atorvastatin	5965 (26.4)

*β-Blocker and flecainide were included as control groups as they are not expected to have significant drug-drug interaction with non–vitamin K oral anticoagulants.

P<0.01*), digoxin (adjusted HR, 1.30 [95% CI, 1.13–1.51]; *P*<0.01*), diltiazem (adjusted HR, 1.18 [95% CI, 1.01–1.39]; *P*=0.04*), clarithromycin (adjusted HR, 4.98 [95% CI, 3.87–6.42]; *P*<0.01*), and fluconazole (adjusted HR, 2.38 [95% CI, 1.23–4.59]; *P*=0.02*) were associated with increased gastrointestinal bleeding risk. Interestingly, concomitant atorvastatin use was associated with reduced gastrointestinal bleeding risk (adjusted HR, 0.79 [95% CI, 0.67–0.92]; *P*<0.01*). On univariate analysis, dronedarone was associated with possible reduced risk of gastrointestinal bleeding. However, further analysis using multivariate approach revealed that dronedarone had no significant impact on gastrointestinal bleeding risk (*P*=0.20). No significant differences were observed among patients taking β-blocker or flecainide, which served as control groups (Table 3) (Figure 2). As tartaric acid coating of dabigatran can irritate the gastrointestinal tract, further analysis was performed to investigate its effect on gastrointestinal bleeding. Unexpectedly, possible antagonistic statistical interaction was found between dabigatran and clarithromycin (*P*=0.03*). No statistical interaction between dabigatran and the other tested medications was observed.

Intracranial Hemorrhage

A total of 266 patients (1.18%) experienced intracranial hemorrhage during the follow-up period. Among concomitant medications with potential pharmacokinetic and pharmacodynamic effects leading to increased bleeding risk, only amiodarone (adjusted HR, 2.20 [95% CI, 1.64–2.94]; *P*<0.01*) and digoxin (adjusted HR, 1.61 [95% CI, 1.21–2.15]; *P*<0.01*) were associated with increased risk of intracranial hemorrhage, after adjusting for confounding factors, including the use of antiplatelet agents. No significant differences were observed among patients in the control groups (Table 3) (Figure 3).

Hospitalization for Major Bleeding

Hospitalization for major bleeding was defined in this study as hospital admission attributable to gastrointestinal bleeding and/or intracranial hemorrhage. In total, 1362 (6.04%) patients required hospitalization for the prespecified bleeding events. After adjusting for confounding factors, amiodarone (adjusted HR, 1.64 [95% CI, 1.43–1.88]; *P*<0.01*), digoxin (adjusted HR, 1.35 [95% CI, 1.18–1.54]; *P*<0.01*), clarithromycin (adjusted HR, 4.18 [95% CI, 3.26–5.35]; *P*<0.01*), and fluconazole (adjusted HR, 2.40 [95% CI, 1.32–4.34]; *P*<0.01*) were associated with increased risk for hospitalization for major bleeding. Although digoxin is known to interact with amiodarone in vivo, there was no observable statistical interaction between the 2 medications on hospitalization for bleeding (*P*=0.55). Interestingly, concomitant atorvastatin use was associated with lower hospitalization for bleeding risk (adjusted HR, 0.86 [95% CI, 0.75–0.98]; *P*=0.03*) (Table 3). Control groups, including β-blockers and flecainide, did not show significant changes in hospitalization for bleeding (Figure 4). Further analysis was performed to evaluate the interaction between choice of NOAC (namely, direct thrombin inhibitor versus factor Xa inhibitor) with the risk of hospitalization for major bleeding. No statistical interaction was observed with all the medications with potential drug-drug interaction with NOAC (Table S3).

All-Cause Mortality

In total, 3151 patients (14.0%) died during the follow-up period. Several concomitant medications were associated with increased risk of all-cause mortality at multivariate analysis, including amiodarone (adjusted HR, 2.65 [95% CI, 2.44–2.86]; *P*<0.01*), digoxin (adjusted HR, 1.85 [95% CI, 1.71–2.01]; *P*<0.01*), diltiazem (adjusted HR, 1.44 [95% CI, 1.31–1.57]; *P*<0.01*), verapamil (adjusted HR, 1.80 [95% CI, 1.35–2.52]; *P*<0.01*), antidepressants (adjusted HR, 1.31 [95% CI, 1.17–1.48]; *P*<0.01*), and fluconazole (adjusted HR, 3.27 [95% CI, 2.34–4.56]; *P*<0.01*) (Table 3) (Figure 5). Given that amiodarone is known to interact with digoxin,[20] we tested for any statistical interaction between the 2 drugs on all-cause mortality. Although both drugs independently increased mortality risk (amiodarone crude HR, 2.84; and digoxin crude HR, 1.93), the crude interaction term was 0.70 (95% CI, 0.60–0.82; *P*<0.01*), suggesting an unexpected antagonistic effect.

Table 3. Adverse Outcomes

Outcome	Without concomitant medication, n/total (%)	With concomitant medication, n/total (%)	Crude HR (95% CI)[†]	*P* value[†]	Adjusted HR (95% CI)[‡]	*P* value[‡]
Gastrointestinal bleeding						
Antiarrhythmic drugs						
Amiodarone	882/19425 (4.54)	231/3143 (7.35)	1.63 (1.41–1.88)	<0.01*	1.53 (1.31–1.78)	<0.01*
β-Blocker[§]	675/14155 (4.77)	438/8413 (5.21)	1.03 (0.91–1.16)	0.67	0.98 (0.85–1.13)	0.74
Digoxin	837/18278 (4.58)	276/4290 (6.43)	1.35 (1.18–1.55)	<0.01*	1.30 (1.13–1.51)	<0.01*
Diltiazem	915/19321 (4.74)	198/3247 (6.10)	1.22 (1.05–1.43)	0.01*	1.18 (1.01–1.39)	0.04*
Dronedarone	1098/22120 (4.96)	15/448 (3.35)	0.58 (0.35–0.97)	0.04*	0.68 (0.39–1.21)	0.20
Flecainide[§]	1107/22377 (4.95)	6/191 (3.14)	0.59 (0.26–1.32)	0.20	0.80 (0.30–2.14)	0.65
Verapamil	1104/22388 (4.93)	9/180 (5.00)	0.94 (0.49–1.82)	0.86	0.87 (0.41–1.83)	0.72
Antidepressants	999/20852 (4.79)	114/1716 (6.64)	1.32 (1.09–1.60)	<0.01*	1.17 (0.95–1.45)	0.13
Antimicrobial						
Clarithromycin	1034/22286 (4.64)	79/282 (28.0)	5.80 (4.61–7.29)	<0.01*	4.98 (3.87–6.42)	<0.01*
Erythromycin	1110/22544 (4.92)	3/24 (12.5)	2.43 (0.78–7.54)	0.13	2.46 (0.79–7.65)	0.12
Fluconazole	1103/22486 (4.91)	10/82 (12.2)	2.69 (1.44–5.02)	<0.01*	2.38 (1.23-4.59)	0.01*
Other azoles	1104/22458 (4.92)	9/110 (8.18)	1.52 (0.79–2.93)	0.21	1.37 (0.68–2.74)	0.38
Atorvastatin	865/16603 (5.21)	248/5965 (4.16)	0.76 (0.66–0.87)	<0.01*	0.79 (0.67–0.92)	<0.01*
Intracranial hemorrhage						
Antiarrhythmic drugs						
Amiodarone	198/19425 (1.02)	68/3143 (2.16)	2.08 (1.58–2.74)	<0.01*	2.20 (1.64–2.94)	<0.01*
β-Blocker[§]	157/14155 (1.11)	109/8413 (1.30)	1.08 (0.85–1.38)	0.53	0.98 (0.73–1.32)	0.91
Digoxin	193/18278 (1.06)	73/4290 (1.7)	1.52 (1.16–1.99)	<0.01*	1.61 (1.21–2.15)	<0.01*
Diltiazem	227/19321 (1.17)	39/3247 (1.2)	0.95 (0.67–1.33)	0.76	0.98 (0.68–1.40)	0.90
Dronedarone	263/22120 (1.19)	3/448 (0.67)	0.48 (0.15–1.49)	0.20	0.76 (0.24–2.40)	0.65
Flecainide[§]	265/22377 (1.18)	1/191 (0.52)	0.41 (0.06–2.94)	0.38	0.89 (0.12–6.43)	0.91
Verapamil	261/22388 (1.17)	5/180 (2.78)	2.18 (0.90–5.29)	0.08	2.32 (0.86–6.24)	0.10
Antidepressants	236/20852 (1.13)	30/1716 (1.75)	1.43 (0.98–2.09)	0.07	1.35 (0.88–2.05)	0.17
Antimicrobial						
Clarithromycin	262/22286 (1.18)	4/282 (1.42)	0.96 (0.36–2.57)	0.93	0.79 (0.25–2.47)	0.69
Erythromycin	265/22544 (1.18)	1/24 (4.17)	3.09 (0.43–22.0)	0.26	3.30 (0.46–23.7)	0.24
Fluconazole	264/22486 (1.17)	2/82 (2.44)	2.17 (0.54–8.72)	0.28	2.18 (0.54–8.77)	0.27
Other azoles	264/22458 (1.18)	2/110 (1.82)	1.34 (0.33–5.40)	0.68	1.37 (0.34–5.53)	0.66
Atorvastatin	180/16603 (1.08)	86/5965 (1.44)	1.26 (0.97–1.63)	0.08	1.22 (0.91–1.63)	0.19
Hospitalization for major bleeding						
Antiarrhythmic drugs						
Amiodarone	1069/19425 (5.50)	293/3143 (9.32)	1.70 (1.50–1.94)	<0.01*	1.64 (1.43–1.88)	<0.01*
β-Blocker[§]	823/14155 (5.81)	539/8413 (6.41)	1.03 (0.93–1.15)	0.55	0.98 (0.86–1.11)	0.71
Digoxin	1021/18278 (5.59)	341/4290 (7.95)	1.37 (1.21–1.55)	<0.01*	1.35 (1.18–1.54)	<0.01*
Diltiazem	1130/19321 (5.85)	232/3247 (7.15)	1.16 (1.00–1.33)	0.04*	1.14 (0.98–1.32)	0.09
Dronedarone	1344/22120 (6.08)	18/448 (4.02)	0.57 (0.36–0.90)	0.02*	0.71 (0.42–1.18)	0.18
Flecainide[§]	1355/22377 (6.06)	7/191 (3.66)	0.56 (0.27–1.18)	0.13	0.82 (0.34–1.99)	0.67
Verapamil	1349/22388 (6.03)	13/180 (7.22)	1.11 (0.64–1.91)	0.71	1.13 (0.63–2.06)	0.68
Antidepressants	1220/20852 (5.85)	142/1716 (8.28)	1.35 (1.13–1.60)	<0.01*	1.20 (1.01–1.45)	0.06
Antimicrobial						
Clarithromycin	1280/22286 (5.74)	82/282 (29.1)	4.84 (3.87–6.05)	<0.01*	4.18 (3.26–5.35)	<0.01*
Erythromycin	1359/22544 (6.03)	3/24 (12.5)	1.99 (0.64–6.19)	0.23	2.05 (0.66–6.37)	0.22
Fluconazole	1350/22486 (6.00)	12/82 (14.6)	2.65 (1.50–4.68)	<0.01*	2.40 (1.32–4.34)	<0.01*
Other azoles	1351/22458 (6.02)	11/110 (10.0)	1.51 (0.84–2.74)	0.17	1.39 (0.74–2.59)	0.30
Atorvastatin	1033/16603 (6.22)	329/5965 (5.52)	0.84 (0.74–0.95)	<0.01*	0.86 (0.75–0.98)	0.03*

(*Continued*)

Table 3. Continued

Outcome	Without concomitant medication, n/total (%)	With concomitant medication, n/total (%)	Crude HR (95% CI)†	*P* value†	Adjusted HR (95% CI)‡	*P* value‡
All-cause mortality						
Antiarrhythmic drugs						
Amiodarone	2148/19425 (11.1)	1003/3143 (31.9)	2.84 (2.63–3.06)	<0.01*	2.65 (2.44–2.86)	<0.01*
β-Blocker§	2048/14155 (14.5)	1103/8413 (13.1)	0.84 (0.78–0.91)	<0.01	0.80 (0.73–0.87)	<0.01*
Digoxin	2132/18278 (11.7)	1019/4290 (23.8)	1.93 (1.79–2.08)	<0.01*	1.85 (1.71–2.01)	<0.01*
Diltiazem	2481/19321 (12.8)	670/3247 (20.6)	1.50 (1.38–1.64)	<0.01*	1.44 (1.31–1.57)	<0.01*
Dronedarone	3131/22120 (14.2)	20/448 (4.46)	0.27 (0.17–0.42)	<0.01*	0.56 (0.36–0.87)	0.01*
Flecainide§	3143/22377 (14.1)	8/191 (4.19)	0.28 (0.14–0.56)	<0.01	0.72 (0.32–1.61)	0.42
Verapamil	3104/22388 (13.9)	47/180 (26.1)	1.73 (1.30–2.31)	<0.01*	1.80 (1.35–2.52)	<0.01*
Antidepressants	2795/20852 (13.4)	356/1716 (20.7)	1.44 (1.29–1.61)	<0.01*	1.31 (1.17–1.48)	<0.01*
Antimicrobial						
Clarithromycin	3098/22286 (13.9)	53/282 (18.8)	1.09 (0.83–1.44)	0.52	0.99 (0.73–1.33)	0.95
Erythromycin	3144/22544 (13.9)	7/24 (29.2)	1.77 (0.84–3.71)	0.13	1.34 (0.60–3.00)	0.47
Fluconazole	3113/22486 (13.8)	38/82 (46.3)	3.49 (2.54–4.81)	<0.01*	3.27 (2.34–4.56)	<0.01*
Other azoles	3125/22458 (13.9)	26/110 (23.6)	1.50 (1.02–2.21)	0.04*	1.27 (0.84–1.92)	0.25
Atorvastatin	2434/16603 (14.7)	717/5965 (12.0)	0.78 (0.72–0.85)	<0.01*	0.86 (0.78–0.94)	<0.01*

HR indicates hazard ratio.
*Indicates statistically significant $P<0.05$.
†Crude HR and 95% CI were calculated using Cox proportional hazard model.
‡Adjusted HR was calculated with adjustment of sex, age, estimated glomerular filtration rate, and presence of hypertension, hyperlipidemia, diabetes, ischemic heart disease, heart failure, stroke, CHA_2DS_2-VASc score, antiplatelets, and NSAID.
§β-Blocker and flecainide were included as control groups as they are not expected to have significant drug-drug interaction with non–vitamin K oral anticoagulants.

Conversely, dronedarone (adjusted HR, 0.56 [95% CI, 0.36–0.87]; *P*=0.01*), atorvastatin (adjusted HR, 0.86 [95% CI, 0.78–0.94]; *P*<0.01*), and β-blocker (adjusted HR, 0.80 [95% CI, 0.73–0.87]; *P*<0.01*) were associated with significant reduction in all-cause mortality risk after adjusting for confounding factors (Table 3) (Figure 5). For patients taking dronedarone, apixaban and edoxaban were preferred to dabigatran and rivaroxaban, according to the guidelines on NOAC use.[12] Further analysis of our data set revealed that among patients who concurrently received dronedarone and NOAC, 47.8% took apixaban, 24.6% took dabigatran, 19.0% took rivaroxaban, and 8.71% took edoxaban. Our study involved data up to 2020, which preceded the European Heart Rhythm Association guideline released in 2021. Subgroup analysis revealed concomitant use of dronedarone and apixaban was associated with lower risk of all-cause mortality with adjusted HR of 0.43 (95% CI, 0.21–0.87) and *P*=0.02*, consistent with finding from the combined cohort. There was no significant association in dabigatran (*P*=0.71), rivaroxaban (*P*=0.51), and edoxaban (*P*=0.99) subgroups. No statistical interaction between dronedarone and digoxin was observed (*P*=0.17).

Sensitivity Analysis

The sensitivity analysis, which restricted follow-up duration to 1 year, showed findings largely consistent with the main study results (Table S4). Erythromycin was associated with increased intracranial hemorrhage at 1 year (adjusted HR, 8.65; *P*=0.03*), although this association was not observed in the full duration cohort. Similarly, elevated hospitalization rates for bleeding were found at 1 year with diltiazem (adjusted HR, 1.29; *P*=0.01*), antidepressants (adjusted HR, 1.29; *P*=0.04*), and erythromycin (adjusted HR, 3.66; *P*=0.03*), but these associations did not persist in the full duration analysis. Although not reaching statistical significance, there were trends toward higher all-cause mortality with verapamil (*P*=0.05) at 1 year, although statistical significance was not reached. All other findings from the 1-year sensitivity analysis remained consistent with the main study results.

DISCUSSION

In this territory-wide real-world retrospective cohort study, we demonstrated that a large proportion of patients with NVAF prescribed an NOAC were also prescribed other concomitant medications for their underlying coexistent medical illness. After adjusting for underlying cardiovascular conditions, multiple concomitant interacting medications prescribed to patients with NVAF treated with an NOAC were associated with increased risks of bleeding events and all-cause

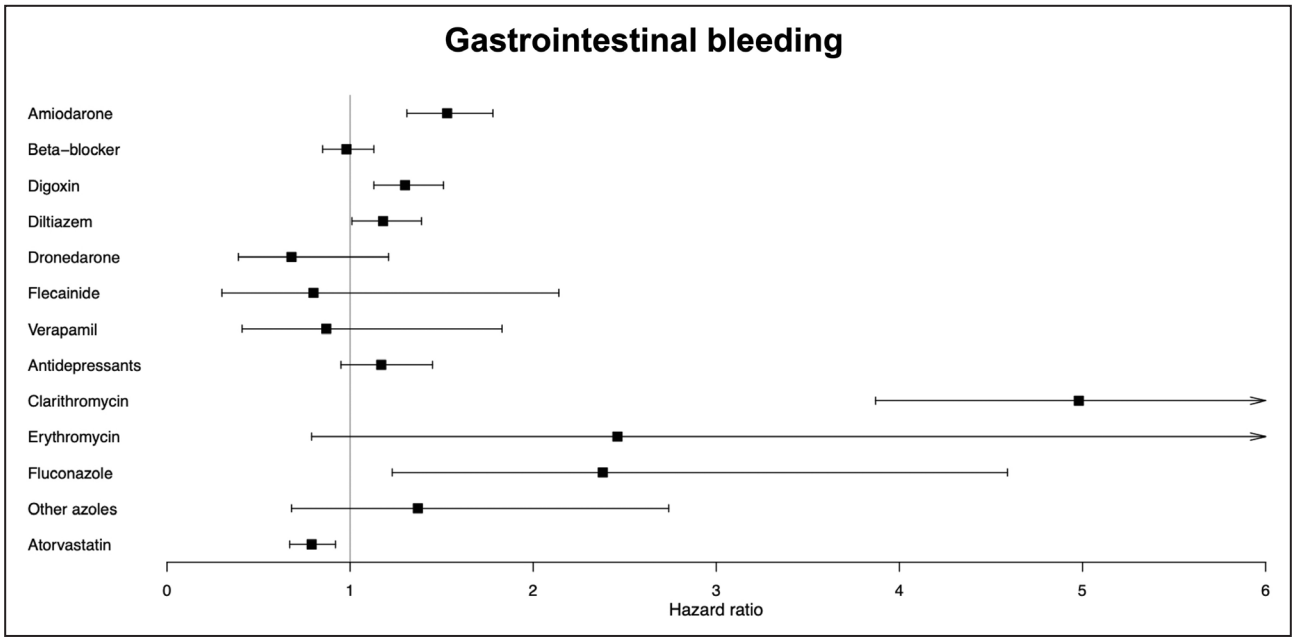

Figure 2. **Forest plot for hazard ratio of gastrointestinal bleeding.**

mortality. Among these concomitant medications, amiodarone and digoxin were consistently associated with increased risks of gastrointestinal bleeding, intracranial hemorrhage, hospitalization for major bleeding, and all-cause mortality in patients with NVAF prescribed an NOAC. Conversely, dronedarone and atorvastatin were associated with reduced risk of all-cause mortality.

In this study, bleeding outcomes analyzed included gastrointestinal bleeding, intracranial hemorrhage, and hospitalization for intracranial hemorrhage and/or gastrointestinal bleeding. These outcomes are comparable to those of other real-world cohort studies.[21,22] Owing to practicality, bleeding outcomes in studies based on electronic medical records are commonly defined using diagnostic codes, such as *ICD-9*, instead of directly implementing bleeding criteria used in clinical trials, such as Bleeding Academic Research Consortium.[23]

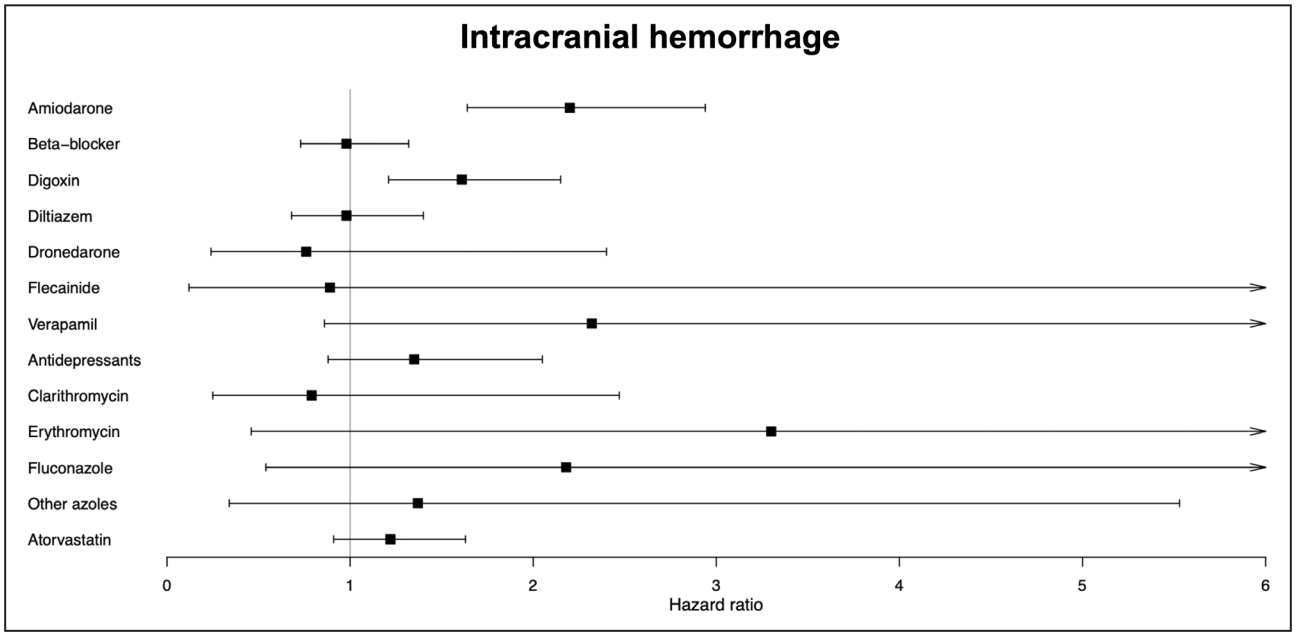

Figure 3. **Forest plot for hazard ratio of intracranial hemorrhage.**

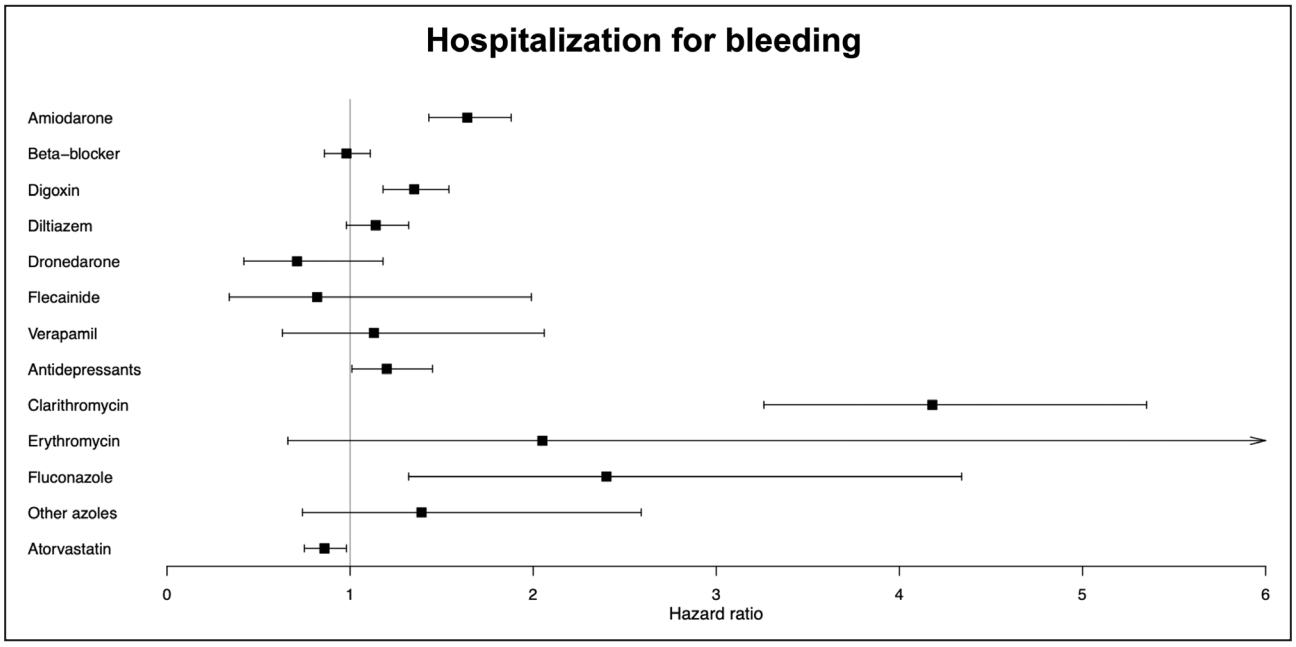

Figure 4. **Forest plot for hazard ratio of hospitalization for bleeding.**

Diltiazem is a weak inhibitor of CYP3A4 and P-glycoprotein, which may increase plasma level of NOACs. Previous guidelines do not regard its concomitant use with NOACs to be associated with high bleeding risk.[12] However, recent national observational studies from both the United States and Belgium demonstrated higher bleeding risk when diltiazem is used in conjunction with NOACs.[15,16] Similarly, we observed higher gastrointestinal bleeding and all-cause mortality rate among patients treated with both diltiazem and NOACs. As diltiazem is commonly used for rate control among patients with AF, it is crucial to conduct further studies to evaluate the safety profile of the drug combination.

Clarithromycin and fluconazole are moderate to strong CYP3A4 inhibitors, in addition to inhibiting

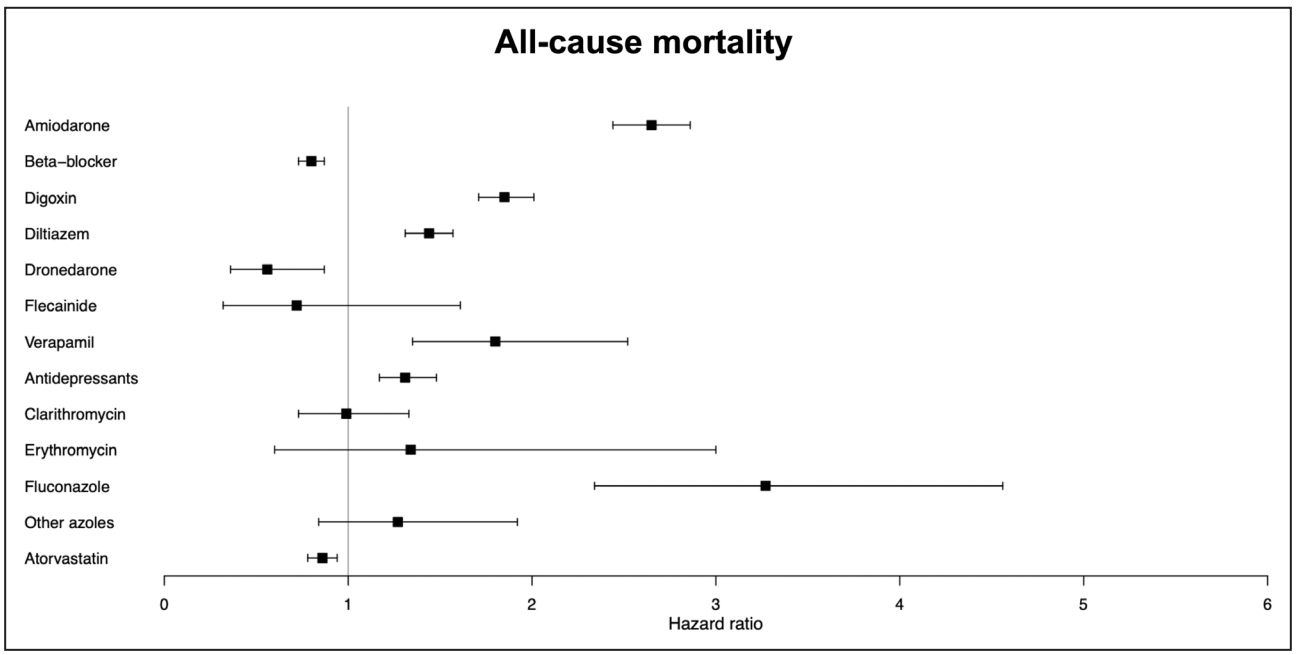

Figure 5. **Forest plot for hazard ratio of all-cause mortality.**

P-glycoprotein.[12] In our propensity score–matched retrospective analysis, they were found to increase the risk of gastrointestinal bleeding and hospitalization for bleeding. When interpreting these results, it is crucial to recognize that prescription of clarithromycin and fluconazole may bias the patient cohort toward those with higher gastrointestinal bleeding risk as clarithromycin is known to be a component of triple therapy for treating *Helicobacter pylori* infection, which may be associated with upper gastrointestinal bleeding, and fluconazole is primarily used by patients with immunosuppressive states.

Amiodarone is a class III antiarrhythmic drug that is used for AF rhythm control. It is a strong CYP3A4 inhibitor and can be expected to significantly increase the plasma concentration of concomitant NOACs.[12] To date, there have been few studies of the effect of concomitant prescription of amiodarone with an NOAC. It has been previously reported that amiodarone did not increase bleeding risk but increased all-cause mortality.[24] Our study comprises one of the largest cohorts of patients concurrently prescribed amiodarone and an NOAC and revealed an association with increased risk of gastrointestinal bleeding (adjusted HR, 1.55), intracranial hemorrhage (adjusted HR, 2.18), hospitalization for bleeding (adjusted HR, 1.66), and all-cause mortality (adjusted HR, 2.64).

Both digoxin and NOACs are P-glycoprotein substrates. Pharmacokinetic studies demonstrate a 16% increased edoxaban peak serum concentration and 21% increased anti-Xa activity.[25] Unexpectedly, previous cohort studies suggested concomitant digoxin prescription reduced bleeding incidence among NOAC users.[14] Our cohort study provided additional data to clarify the effect of concomitant digoxin and NOAC use and found that digoxin was associated with increased risk of gastrointestinal bleeding (adjusted HR, 1.31), intracranial hemorrhage (adjusted HR, 1.61), hospitalization for bleeding (adjusted HR, 1.35), and all-cause mortality (adjusted HR, 1.87).

In addition to pharmacokinetic considerations, pharmacodynamic interactions of concomitantly prescribed medications are also critical in determining overall safety profile. Selective serotonin reuptake inhibitors, one of the most commonly prescribed antidepressants with CYP inhibitory effects,[26] also impair platelet function by multiple mechanisms. As serotonin in platelets is implicated in maintaining platelet hemostatic function, blocking serotonin uptake by platelets results in serotonin depletion and impaired platelet aggregation.[27] Previous studies demonstrated conflicting results on bleeding risk among patients concomitantly taking antidepressants and NOACs.[28,29] Our real-world data demonstrated that antidepressants (adjusted HR, 1.22) were associated with increased hospitalization for bleeding risk, highlighting the potential additive pharmacodynamic effects with an NOAC.

Most guidelines for NOAC drug-drug interaction have been formulated on the basis of CYP and other pharmacokinetic properties and their consequent effects on drug plasma concentration.[12] Nevertheless in vivo drug-drug interactions are notably more complicated than just hepatic metabolism and pharmacokinetic considerations because additive pharmacodynamic effects also lead to an increased risk of adverse effects. With only a small amount of published data on the real-world safety and profile of NOAC use with concomitant medications, existing guidelines issued by cardiology societies provide relatively limited guidance beyond predicted pharmacokinetic considerations.[13,14] The data presented in this study are intended to fill this clinically important knowledge gap. Understandably, it may be occasionally necessary to prescribe medications that are known to interact with an NOAC when there is no alternative therapeutic option. It is critical for clinicians to be vigilant of the increased risk of bleeding and even all-cause mortality when these combination therapies are prescribed, especially for drugs that have been consistently shown by real-world data to worsen outcome.

This study revealed a notable association with reduced all-cause mortality among patients concomitantly treated with dronedarone (adjusted HR, 0.56), atorvastatin (adjusted HR, 0.86), and β-blocker (adjusted HR, 0.80). This aligns with earlier clinical trial findings that highlighted a positive impact on overall survival for patients with cardiovascular disease. Specifically, in A Trial with Dronedarone to Prevent Hospitalization or Death in Patients with Atrial Fibrillation (ATHENA), it was demonstrated that dronedarone reduced risk of incidence of hospitalization attributable to cardiovascular events or death with high-risk AF.[30] Similarly, atorvastatin was shown to reduce the risk of composite cardiovascular outcomes among patients with stable coronary artery disease.[31] Our study affirms that although dronedarone and atorvastatin interact with P-glycoprotein and CYP3A4, it is overall still beneficial and safe to use them in conjunction with NOAC. On the other hand, the effect of β-blocker on patients with AF is more controversial. Although there has not been a dedicated randomized controlled trial comparing β-blockers with placebo in patients with AF, trials that included β-blockers, such as the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE) II trial, which compared stringent versus lenient rate control, did not show a significant survival benefit.[32] There was real-world observational study indicating a potential reduction in all-cause mortality among patients taking β-blockers, with or without heart failure.[33]

Data from a population-based cohort study from Sweden demonstrated trend toward dabigatran having less interaction than the analyzed factor Xa inhibitors with respect to bleeding outcomes.[34] In our study, the

use of direct thrombin inhibitors, as opposed to factor Xa inhibitor, was not found to be significantly associated with increased bleeding risk.

LIMITATIONS

This study has several limitations: First, as this is a retrospective cohort analysis instead of prospective randomized controlled trial, the observed effects of NOAC and concomitant mediation represent statistical association, rather than imply causality. Prospective studies are required to generate definitive conclusions. Second, as information about patients' body weight was not available, appropriate, and inappropriate dosage adjustment of NOAC could not be determined in our study. Third, there is a lack of detailed analysis of periods of exposure to concomitant medications. Future research may address this by considering varying durations of concomitant medication use to better understand potential interactions and their clinical implications. Fourth, owing to the lack of information on blood pressure values and alcohol use, it was not possible to accurately calculate hypertension, abnormal renal/ liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/ alcohol concomitantly (HAS-BLED) score for each subject. Fifth, β-blocker and flecainide were included in the study as control as they are commonly prescribed together with NOAC and have no known significant drug-drug interactions. Although multivariate Cox regression was performed to adjust for differences in baseline characteristics, differences in baseline demographics and cardiovascular risk factor profile, as summarized in Table S2, may affect the conclusion derived. Sixth, the number of patients in some medication groups was small, such as erythromycin and fluconazole. Further studies involving more patients is required to ensure generalizability of the corresponding findings.

CONCLUSIONS

In this real-world clinical practice, the use of an NOAC with concomitant drug-drug interaction was associated with bleeding risk and mortality in patients with NVAF.

ARTICLE INFORMATION

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Acknowledgments

Author contributions: HFT and KKL contributed to the conception and design of the study. YKW performed data acquisition. CKW, YKW, YHC, ML, JSHH, KHY, GYHL, KKL, and HFT performed data analysis and interpretation. CKW, YKW, and ML wrote the first draft of the manuscript. YHC, JSHH, KHY, GYHL, KKL, and HFT revised the manuscript critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published.

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Disclosures

None.

Supplemental Material

Tables S1–S4

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