

Effect of drug interactions with non-vitamin-K oral anticoagulants on thromboembolic events in patients with nonvalvular atrial fibrillation

Jin-Hua Chen^{*1,2,3} PhD, Ming-Chia Lee^{*4,5,6} PhD, Tzu-Hsin Yen⁴ MS, Pei-Yu Huang⁴ MS, De-En Lu^{7,8} MD, Chih-Hsin Lee^{8,9,10} MD, Hsien-Chen Chang^{8,9} BS, Jann-Yuan Wang¹¹ MD, Jen-Ai Lee⁴ PhD

ABSTRACT

Introduction: Few real-world studies have investigated drug-drug interactions (DDIs) involving non-vitamin-K antagonist oral anticoagulants (NOACs) in patients with nonvalvular atrial fibrillation (NVAF). The interactions encompass drugs inducing or inhibiting cytochrome P450 3A4 and permeability glycoprotein. These agents potentially modulate the breakdown and elimination of NOACs. This study investigated the impact of DDIs on thromboembolism in this clinical scenario.

Method: Patients who had NVAF and were treated with NOACs were selected as the study cohort from the National Health Insurance Research Database of Taiwan. Cases were defined as patients hospitalised for a thromboembolic event and who underwent a relevant imaging study within 7 days before hospitalisation or during hospitalisation. Each case was matched with up to 4 controls by using the incidence density sampling method. The concurrent use of a cytochrome P450 3A4/permeability glycoprotein inducer or inhibitor or both with NOACs was identified. The effects of these interactions on the risk of thromboembolic events were examined with univariate and multivariate conditional logistic regressions.

Results: The study cohort comprised 60,726 eligible patients. Among them, 1288 patients with a thromboembolic event and 5144 matched control patients were selected for analysis. The concurrent use of a cytochrome P450 3A4/permeability glycoprotein inducer resulted in a higher risk of thromboembolic events (adjusted odds ratio [AOR] 1.23, 95% confidence interval [CI] 1.004–1.51).

Conclusion: For patients with NVAF receiving NOACs, the concurrent use of cytochrome P450 3A4/permeability glycoprotein inducers increases the risk of thromboembolic events.

Ann Acad Med Singap 2024;53:69-79

Keywords: drug-drug interaction, nonvalvular atrial fibrillation, non-vitamin-K antagonist oral anticoagulant, thromboembolic event

CLINICAL IMPACT

What is New

- For patients with nonvalvular atrial fibrillation (NVAF) receiving non-vitamin-K antagonist oral anticoagulants (NOACs), the concurrent use of cytochrome P450 3A4/permeability glycoprotein inducers increases the risk of thromboembolic events.

Clinical Implication

- Healthcare professionals should avoid prescribing cytochrome P450 3A4/permeability glycoprotein inducers to patients with NVAF who are taking NOACs.

INTRODUCTION

Atrial fibrillation (AF), a type of arrhythmia for which the incidence and prevalence are rising in the older population, has become a global epidemic.¹ The estimated prevalence of AF is approximately 2% to 4%,^{2,3} and its prevalence is projected to increase by 2.3-fold by 2030.³ Older patients with AF have a substantial risk of ischaemic

The Annals is an open access journal, allowing non-commercial use under CC BY-NC-SA 4.0.

¹ Biostatistics Center, College of Management, Taipei Medical University, Taipei, Taiwan

² Graduate Institute of Data Science, College of Management, Taipei Medical University, Taipei, Taiwan

³ Department of Medical Education and Research, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

⁴ School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan

⁵ Department of Pharmacy, New Taipei City Hospital, New Taipei City, Taiwan

⁶ Department of Nursing, Cardinal Tien College of Healthcare and Management, Taipei, Taiwan

⁷ Division of Nephrology, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

⁸ Pulmonary Research Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

⁹ Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

¹⁰ Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

¹¹ Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

* Joint first authors

Correspondence: Dr Chih-Hsin Lee, Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.

Email: chleedtw@tmu.edu.tw

stroke, with this risk being 5 times that of the healthy population.^{1,4} Ischaemic stroke is a leading cause of death globally. Moreover, the subsequent disabilities may adversely affect the quality of life of ischaemic stroke survivors and their families.⁵⁻⁷ Hence, early diagnosis and stroke prevention therapy are the utmost priority in the management of AF.

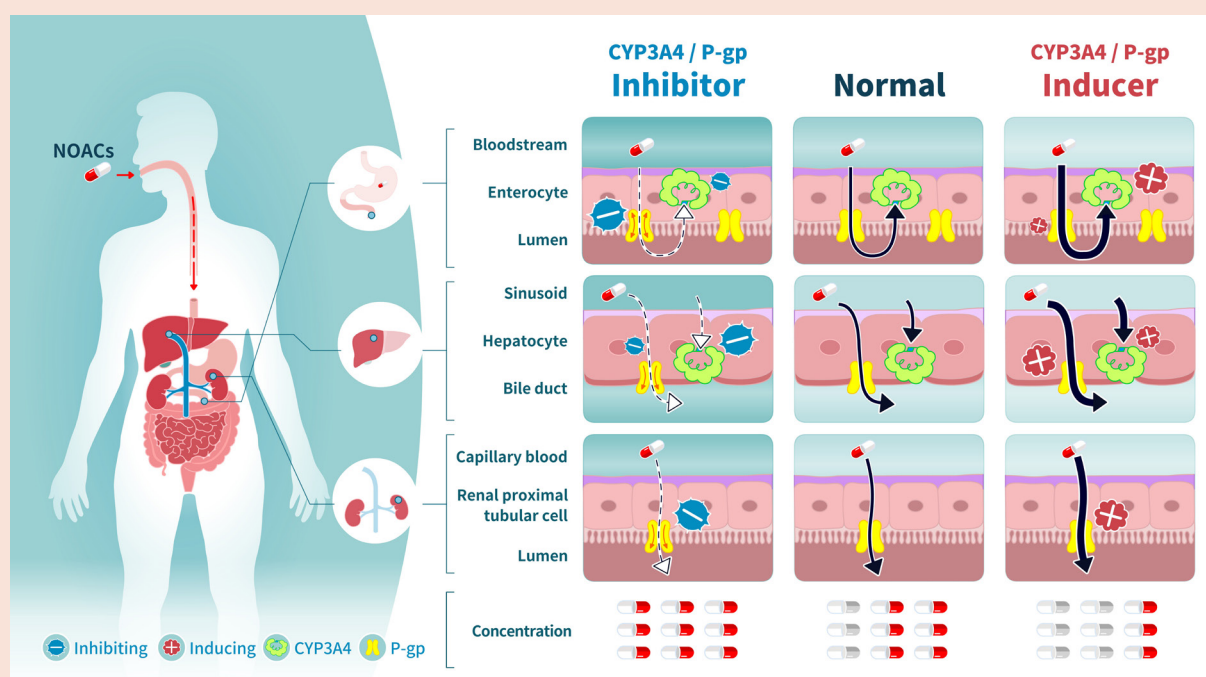
Non-vitamin-K antagonist oral anticoagulants (NOACs) are increasingly being administered to patients with nonvalvular AF (NVAf), essentially replacing warfarin as a means of preventing ischaemic stroke and extracranial embolism because NOACs have superior efficacy and safety compared with warfarin.⁸⁻¹¹ Furthermore, NOAC users tend to have better adherence than warfarin users because of certain qualities of NOACs: (1) their rapid onset of action and shorter half-life, (2) no requirement of international normalised ratio monitoring, (3) fewer dietary restrictions and (4) fewer drug-drug interactions (DDIs).^{2,12-14} A summary depicting the absorption, metabolism and excretion of NOACs, along with their interactions with cytochrome P450 3A4 (CYP3A4) and permeability glycoprotein (P-gp) inducers or inhibitors, is illustrated in Fig. 1. However, DDIs

involving NOACs occasionally occur, especially in patients with multiple morbidities and polypharmacy.¹⁵ The coadministration of NOACs and medications modifying CYP3A4 and P-gp activity has been reported to substantially alter patients' NOAC exposure.^{16,17}

NOAC users who co-administered 9 or more drugs were determined to have a higher risk of stroke than those who received 5 or fewer drugs (adjusted hazard ratio 1.54, 95% confidence interval [CI] 1.19–1.99) in a post hoc analysis of phase 3 randomised controlled trials involving NOAC use in AF populations.¹⁶ A recent large observational study reported that the concurrent use of NOACs with amiodarone, fluconazole, phenytoin and rifampin was associated with a significantly increased risk of major bleeding.¹⁷ However, phenytoin and rifampin are strong P-gp and CYP3A4 inducers. They reduce the bioavailability of NOACs¹⁸⁻²⁰ and should increase the risk of thromboembolism instead of a bleeding event. As this result contradicted existing evidence, further investigation is required.

Because of research ethics, older individuals and patients with multiple morbidities are usually excluded from randomised controlled trials.²¹

Fig. 1. Summary of absorption, metabolism and excretion of NOACs. Following the oral intake of NOACs, they are absorbed from intestinal to blood stream. P-gp and CYP3A4 are both expressed in the intestinal mucosa and attenuate drug exposure of oral drug delivery. Some NOACs would be transported back to intestine through P-gp and being metabolised by CYP3A4. Furthermore, upon reaching the liver, NOACs are subjected to metabolic transformation by CYP3A4, with P-gp playing a role in expediting their excretion into the biliary system. Finally, NOACs are also eliminated by P-gp in the kidneys. Therefore, CYP3A4/P-gp inducers increase the metabolism or excretion of NOACs, leading to a decrease in their blood concentration. Conversely, CYP3A4/P-gp inhibitors result in an increase in the blood concentration of NOACs.



CYP3A4: cytochrome P450 3A4; NOACs: non-vitamin-K antagonist oral anticoagulants; P-gp: permeability glycoprotein

Real-world drug interaction studies involving these vulnerable populations are thus lacking. Older adults with various comorbidities have become a major issue for those having to make decisions related to AF in clinical practice.¹⁶ Therefore, we conducted this nested case-control study to investigate the effect of interactions between NOACs and P-gp and CYP3A4 modifiers on the risk of thromboembolic events in patients with NVAF.

METHOD

Data acquisition

This nested case-control study was conducted using Taiwan's National Health Insurance Research Database (NHIRD). The National Health Insurance System comprehensively covers nearly 99% of the nationwide population in Taiwan for more than 2 decades. The NHIRD offers a broad and impartial longitudinal population for studying the potential effects of drug interactions involving NOACs on the susceptibility to thromboembolic events. Data from 1 January 2010 to 31 December 2018 were employed to evaluate the impact of DDIs on the protective efficacy of NOACs.

Study cohort

We searched the NHIRD for inpatient and outpatient records containing the diagnosis code for NVAF (International Classification of Diseases, Clinical Modification, 9th Revision code 427.31 or International Classification of Diseases, Clinical Modification, 10th Revision code I48.0, I48.2, I48.91 or I48.1). Adult (age ≥ 20 years) patients who had at least 2 outpatient records or 1 inpatient record of NVAF within a period of 365 days and who were prescribed an NOAC were considered eligible for inclusion. Patients with NVAF who received their first NOAC prescription between 1 January 2012 and 31 December 2017 were enrolled in the study cohort. The Anatomical Therapeutic Chemical (ATC) Classification System codes of NOACs were dabigatran (B01AE07), rivaroxaban (B01AF01 and B01AX06), apixaban (B01AF02 and B01AX08) and edoxaban (B01AF03). We excluded patients who, before the first NOAC prescription date, had mitral stenosis, a prosthetic valve, infective endocarditis or chronic kidney disease and those who had end-stage renal disease or acute renal failure and were undergoing renal replacement therapy. The definitions of the diseases for exclusion are presented in Supplementary Table S1. The flowchart for patient enrolment in this study is displayed in Fig. 2.

Cases with thromboembolic events and control patients

The healthcare records of enrolled patients were scrutinised to identify thromboembolic events. These events included ischaemic stroke, non-specified stroke, transient ischaemic attack, arterial embolism and mesenteric ischaemia. The accuracy of ischaemic stroke diagnosis in the NHIRD was reported to be 94%.²² The positive predictive value and sensitivity of ischaemic stroke identification through diagnosis codes were reported to be 88.4% and 97.3%, respectively.²³ The cases were patients hospitalised for any thromboembolic event and undergoing computerised tomography or magnetic resonance imaging during the 7 days before their hospital admission or during hospitalisation. The index date was defined as the date of diagnosis of the incident thromboembolic event. We matched each case by age, sex and duration since NOAC commencement with up to 4 controls in the study cohort by using the incidence density sampling method. In addition, the proportion of days covered (PDC) of the NOAC during the 3 months before the index date had to be 0.8 or higher. The PDC was defined as the proportion of a given period of interest in which a specified medication was administered to a patient.²⁴

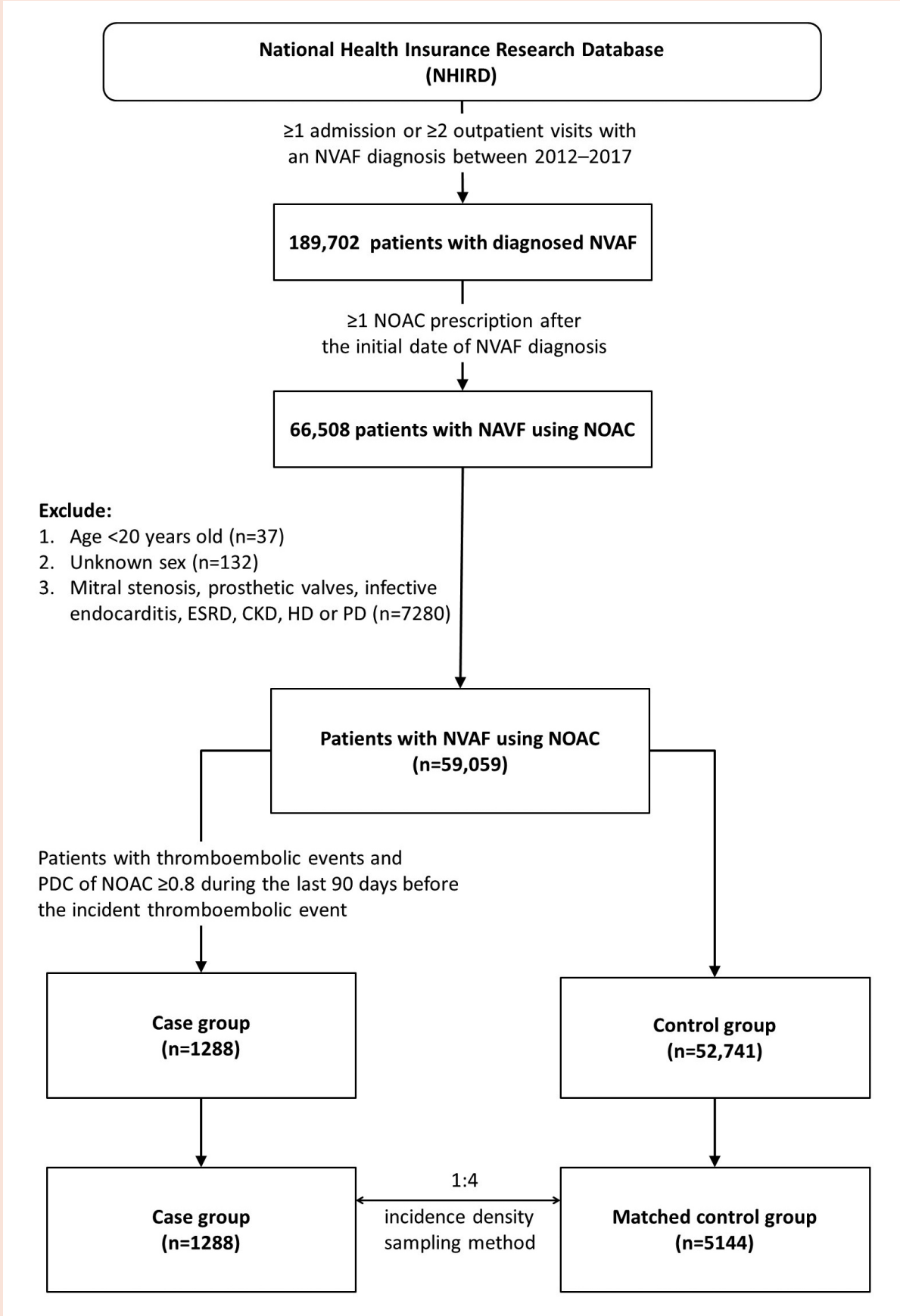
Exposure to NOAC drug interactions

The exposure of interest in this study was NOAC drug interaction, defined as the concurrent use of an NOAC and CYP3A4/P-gp inducers or inhibitors or other medications that affect a patient's effective NOAC exposure. CYP3A4/P-gp inducers, which reduce the concentrations of NOACs, include phenytoin and rifampin. CYP3A4/P-gp inhibitors, which increase the concentrations of NOACs, include fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole, erythromycin, clarithromycin, verapamil, diltiazem, amiodarone, dronedarone and cyclosporine. The ATC codes of medications are presented in Supplementary Table S2. Strong inhibitors (ketoconazole, itraconazole, voriconazole, posaconazole and clarithromycin) and inducers (phenytoin and rifampin) are drugs that increase or reduce the area under the curve of substrates of a given metabolic pathway by >5 -fold and by 80%, respectively.²⁵ The definition of concurrent use was the prescription of any of the mentioned drugs during the 3 months before the index date.

Other confounding factors

We identified patients' baseline characteristics, comorbidities and related medications, which were considered possible confounding factors that could

Fig. 2. Flowchart of study design and case selection.



CKD: chronic kidney disease; ESRD: end-stage renal disease; HD: haemodialysis; NOAC: non-vitamin-K antagonist oral anticoagulant/novel oral anticoagulant; NVAF: nonvalvular atrial fibrillation; PD: peritoneal dialysis; PDC: proportion of days covered

adjust the likelihood of a thromboembolic event. The baseline characteristics were patients' age, sex and income. The comorbidities were hypertension, congestive heart failure, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), malignancy, dyslipidaemia and peripheral arterial occlusive disease (PAOD). We also calculated the CHA₂DS₂VASc score, a risk stratification tool used for anticoagulation decision-making, to adjust our results for the risk of stroke.³ The related medications were considered when more than 90 defined daily dose prescriptions were noted for antiplatelet agents, warfarin, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors and corticosteroids.

Statistical analysis

The paired-sample t-test or McNemar test was used to compare variables between the cases and controls as appropriate. Univariate and multivariate conditional logistic regressions were performed to evaluate the impact of DDIs on the risk of thromboembolic events. The covariates considered were age (≤ 59 versus 60–79 vs ≥ 80 years), sex (female vs male), monthly income ($\leq 16,500$ vs 16,501–26,400 vs $\geq 26,401$ New Taiwan [NT] dollars) and comorbidities in Model 1; age, sex, income and higher risk of stroke (CHA₂DS₂VASc score ≥ 2 for men and ≥ 3 for women) in Model 2; age, sex, income, comorbidities and medication use (warfarin, antiplatelet agents, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, NSAIDs, proton pump inhibitors and corticosteroids) in Model 3; and age, sex, income, higher risk of stroke²⁶ and medication use in Model 4. In sensitivity analysis, only the concurrent use of strong CYP3A4/P-gp inhibitors or inducers was considered to cause an effective DDI. Furthermore, we performed subgroup analyses stratified by sex. Statistical significance was set at 2-sided $P < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, US).

RESULTS

Study cohort, cases and controls

For the period from 2012 to 2017, a total of 66,508 patients with NVAF and taking NOACs were identified in the NHIRD of Taiwan. After applying the exclusion criteria, the number of patients eligible for the study was found to be 59,059. Among these patients, we identified 1288 cases of thromboembolic events where the PDC of NOACs was >0.8 during the 90 days before the

index date; 5144 matched control patients were also selected (Fig. 2).

The baseline characteristics are detailed in Table 1. The mean age was 77.7 ± 9.7 years, and approximately 43% of the patients were older than 80 years. The case and control groups' age, sex and income were similar. Women comprised 51.6% of the case and control groups. Rivaroxaban and dabigatran were the most frequently used NOACs. The prevalence rates of hypertension (93.8% vs 88.7%), congestive heart failure (49.6% vs 43.5%), DM (19.4% vs 15.4%), COPD (9.2% vs 6.7%), dyslipidaemia (8.5% vs 6.7%) and PAOD (3.4% vs 1.4%) were higher in the case group than in the control group.

Exposure to DDIs was significantly different between the case and control groups ($P < 0.001$). Compared with the controls, the cases were more likely to concurrently use a CYP3A4/P-gp inducer (12.4% vs 8.6%).

The CHA₂DS₂VASc score was higher in the case group than in the control group (5.6 ± 2.9 vs 4.3 ± 2.7 , $P < 0.001$). However, more than 90% of the patients in both groups had a high-risk score of CHA₂DS₂VASc. The patients in the case group were more likely to have concurrent exposure to the following other medications: antiplatelet agents (24.1% vs 18.8%, $P < 0.001$), hypoglycaemic agents (18.3% vs 15.5%, $P < 0.001$), insulin (4.4% vs 2.7%, $P < 0.001$), NSAIDs (12.8% vs 11.4%, $P = 0.022$) and proton pump inhibitors (9.6% vs 7.1%, $P < 0.001$).

Association between thromboembolic events and interaction of NOACs with CYP3A4/P-gp modifiers in patients with NVAF

The association between DDIs with NOACs and the risk of thromboembolic events in patients with NVAF is detailed in Table 2. In the univariate analysis, a CYP3A4/P-gp inducer (OR 1.30; 95% CI 1.07–1.59) of DDI was associated with a higher risk of a thromboembolic event. After adjusting the confounding effects of demographics, comorbidities, high-risk scores of strokes, and use of other medications, we obtained consistent results for the 4 models (Table 2), indicating that the concurrent use of a CYP3A4/P-gp inducer carried a higher risk of thromboembolic events. The adjusted odds ratios (AORs) from Models 1 to 4 were 1.26 (95% CI 1.07–1.59), 1.27 (95% CI 1.04–1.56), 1.22 (95% CI 0.997–1.50) and 1.23 (95% CI 1.004–1.51), respectively. Using an NOAC concurrently with CYP3A4/P-gp inhibitors had a marginal effect in reducing the thromboembolic events that the univariate and multivariate analyses all showed point estimates of ORs less than 1. However, only 1 of the 5 models showed statistical significance. Patients using NOACs concurrently with

Table 1. Baseline characteristics of cases and controls.

	Cases with thromboembolic events (n=1288)	Controls without thromboembolic events (n=5144)	P value
Age, mean $\pm$ SD	77.7 $\pm$ 9.7	77.7 $\pm$ 9.6	0.206
≤59 years	64 (5.0%)	245 (4.8%)	0.383
60–79 years	670 (52.0%)	2712 (52.7%)	
≥80 years	554 (43.0%)	2187 (42.5%)	
Female sex	665 (51.6%)	2652 (51.6%)	0.962
Income (NT dollars per month), no. (%)			0.3262
≤16,500	374 (29.0%)	1571 (30.6%)	
16,501–26,400	597 (46.4%)	2290 (44.5%)	
≥26,401	317 (24.6%)	1283 (24.9%)	
Types of NOACs, no. (%)			
Rivaroxaban	656 (50.9%)	2590 (50.4%)	0.127
Dabigatran	522 (40.5%)	1978 (38.5%)	0.011
Apixaban	142 (11.0%)	633 (12.3%)	0.033
Edoxaban	36 (2.8%)	133 (2.6%)	0.394
PDC of each NOAC, mean $\pm$ SD			
Rivaroxaban	0.94 $\pm$ 0.16	0.96 $\pm$ 0.13	0.016
Dabigatran	0.95 $\pm$ 0.14	0.96 $\pm$ 0.14	0.121
Apixaban	0.88 $\pm$ 0.26	0.94 $\pm$ 0.17	0.016
Edoxaban	0.86 $\pm$ 0.28	0.88 $\pm$ 0.23	0.663
Drug-drug interaction, no. (%)			<0.001
No interaction	710 (55.1%)	2821 (54.8%)	
CYP3A4/P-gp, no. (%)			
Inhibitors	349 (27.1%)	1558 (27.4%)	
Inducers	160 (12.4%)	489 (8.6%)	
Inhibitors and inducers	69 (5.4%)	276 (5.0%)	
Comorbidity, no. (%)			
Hypertension	1209 (93.8%)	4560 (88.7%)	<0.001
Congestive heart failure	639 (49.6%)	2235 (43.5%)	<0.001
Diabetes mellitus	250 (19.4%)	794 (15.4%)	<0.001
COPD	119 (9.2%)	346 (6.7%)	<0.001
Malignancy	122 (9.5%)	525 (10.2%)	0.227
Dyslipidaemia	109 (8.5%)	342 (6.7%)	<0.001
PAOD	44 (3.4%)	70 (1.4%)	<0.001

Table 1. Baseline characteristics of cases and controls. (Cont'd)

	Cases with thromboembolic events (n=1288)	Controls without thromboembolic events (n=5144)	P value
CHA ₂ DS ₂ VASc score, mean ± SD	5.6 ± 2.9	4.3 ± 2.7	<0.001
High risk of stroke (≥3 in females, ≥2 in males), no. (%)	1266 (98.2%)	4667 (90.7%)	<0.001
Medication use, no. (%)			
Calcium channel blockers	368 (28.6%)	1461 (28.4%)	0.809
Antiplatelet agents	310 (24.1%)	967 (18.8%)	<0.001
Lipid-lowering agents	285 (22.1%)	731 (23.8%)	0.951
Hypoglycaemic agents	235 (18.3%)	796 (15.5%)	<0.001
NSAIDs	165 (12.8%)	585 (11.4%)	0.022
Proton pump inhibitors	124 (9.6%)	366 (7.1%)	<0.001
Antihypertensive agents	74 (5.8%)	263 (5.1%)	0.145
Corticosteroids	45 (3.5%)	106 (3.1%)	<0.270
Insulin	57 (4.4%)	137 (2.7%)	<0.001
Warfarin	12 (0.9%)	36 (0.7%)	0.185

COPD: chronic obstructive pulmonary disease; NOACs: non-vitamin-K antagonist oral anticoagulants; NSAIDs: nonsteroidal anti-inflammatory drugs; NT dollars: New Taiwan dollars; PAOD: peripheral arterial occlusive disease; PDC: proportion of days covered; SD: standard deviation

both inducers and inhibitors did not increase the risk of thromboembolic events compared to patients without DDIs.

Subgroup analyses stratified by sex and history of thromboembolic events

The results of subgroup analyses stratified by sex and history of thromboembolic events are illustrated in Fig. 3. For male patients, the concurrent use of a CYP3A4/P-gp inhibitor was associated with a reduced risk of a thromboembolic event (AOR 0.77 [95% CI 0.62–0.95]). In addition, the concurrent use of a CYP3A4/P-gp inducer was associated with an increased risk of a thromboembolic event (AOR 1.35 [95% CI 1.01–1.81]). However, for female patients, the concurrent use of CYP3A4/P-gp modifiers, either inhibitors, inducers or both, showed no significant association with the risk of thromboembolic events.

Sensitivity analysis regarding only strong CYP3A4/P-gp inhibitors and inducers

We conducted sensitivity analyses to examine the effects of strong inhibitors and inducers of CYP3A4/P-gp. The AORs of the concurrent use of strong CYP3A4/P-gp inducers for a thromboembolic event (1.96–2.06, Supplementary Table S3) were higher than that in the main scenario (1.22–1.27,

Table 2). The AORs of the concurrent use of a strong CYP3A4/P-gp inhibitor for thromboembolic events were greater than 1, but the 95% CIs were much wider than the results were not significant. In addition, the AORs of a CYP3A4/P-gp inducer or inhibitor among patients using each single NOAC were not associated with the risk of thromboembolic events (Supplementary Tables S4–S7).

The dosing of NOACs, in terms of mean-defined daily doses, among patients prescribed with inhibitors or inducers is similar (Supplementary Table S8). The breakdown of the percentages of types of inhibitors/inducers is described in the supplementary file (Supplementary Table S9).

DISCUSSION

The present study showed that the concurrent use of an NOAC with CYP3A4/P-gp inducers increased the risk of thromboembolic events. The impact of strong CYP3A4/P-gp inducers on thromboembolic events was even higher. To the best of our knowledge, this is the first nested case-control study using an administrative database to investigate the association between NOAC-based DDIs and a thromboembolic event. Suboptimal drug exposure has been proposed in several studies to be the major cause of failure of NOAC-based treatments.^{27,28} The relevant pharmacokinetic

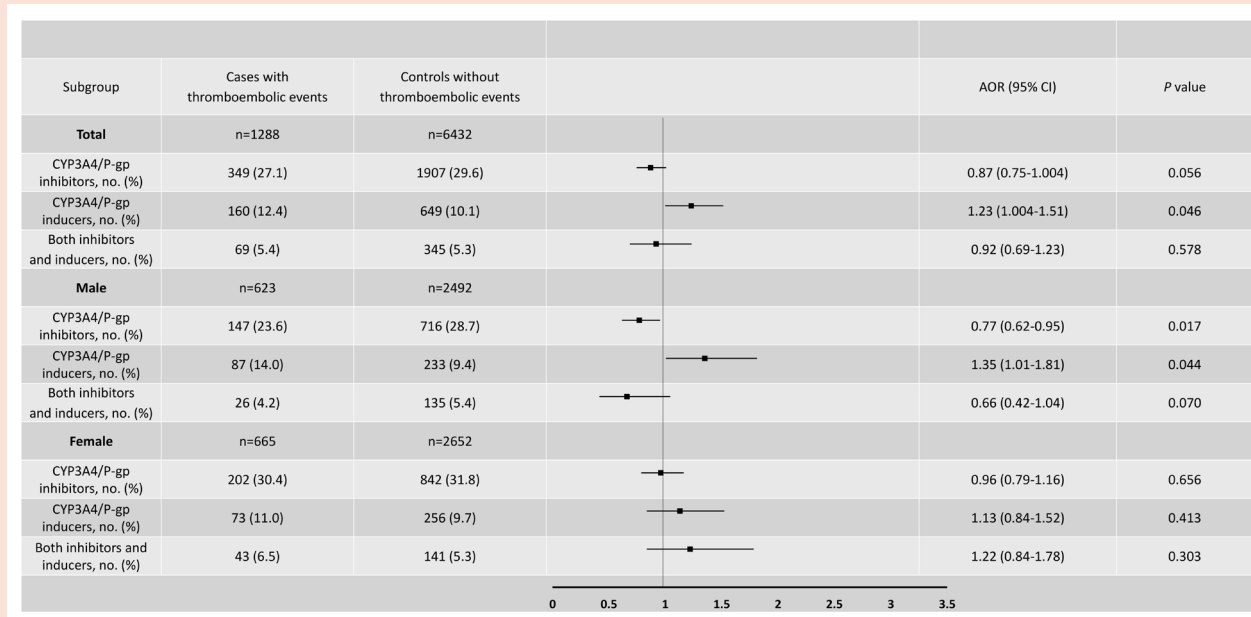
Table 2. Association of the concomitant use of a CYP3A4/P-gp inhibitor or inducer with thromboembolic events.

DDI	Cases with thromboembolic events (n=1288), no. (%)	Controls without thromboembolic events (n=5144), no. (%)	Univariate OR (95% CI)	P value	Model 1 ^a AOR (95% CI)	P value	Model 2 ^b AOR (95% CI)	P value	Model 3 ^c AOR (95% CI)	P value	Model 4 ^d AOR (95% CI)	P value
No DDI	710 (55.1)	3531 (54.8)	1		1		1		1		1	
CYP3A4/P-gp inhibitors	349 (27.1)	1907 (29.6)	0.89 (0.77-1.03)	0.115	0.88 (0.76-1.02)	0.081	0.89 (0.77-1.03)	0.122	0.86 (0.74-0.996)	0.044	0.87 (0.75-1.004)	0.056
CYP3A4/P-gp inducers	160 (12.4)	649 (10.1)	1.30 (1.07-1.59)	0.008	1.26 (1.03-1.54)	0.024	1.27 (1.04-1.56)	0.018	1.22 (0.997-1.50)	0.053	1.23 (1.004-1.51)	0.046
Both	69 (5.4)	345 (5.3)	0.99 (0.75-1.31)	0.967	0.97 (0.73-1.29)	0.829	0.95 (0.72-1.27)	0.746	0.95 (0.71-1.26)	0.706	0.92 (0.69-1.23)	0.578

AOR: adjusted odds ratio; CI: confidence interval; DDI: drug-drug interaction; OR: odds ratio.

^a Adjusted for age, sex, income and comorbidities (hypertension, congestive heart failure, diabetes mellitus, COPD, malignancy, dyslipidaemia and PAOD).^b Adjusted for age, sex, income and high risk of stroke.^c Adjusted for age, sex, income, comorbidities (hypertension, congestive heart failure, diabetes mellitus, COPD, malignancy, dyslipidaemia and PAOD), medication use (warfarin, antiplatelet agents, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, NSAIDs, proton pump inhibitors and corticosteroids).^d Adjusted for age, sex, income, high risk of stroke, medication use (warfarin, antiplatelet agents, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, NSAIDs, proton pump inhibitors and corticosteroids).

Fig. 3. Forest plot of subgroup analysis (odds ratios were adjusted for age, sex, income, high risk of stroke and medication use [warfarin, antiplatelet agents, calcium channel blockers, antihypertensive agents, hypoglycaemic agents, insulin, lipid-lowering agents, NSAIDs, proton pump inhibitors and corticosteroids]).



AOR: adjusted odds ratio; CI: confidence interval

knowledge indicates that CYP3A4/P-gp inducers reduce the plasma levels of NOACs and result in NOAC users having an increased risk of a thromboembolic event. However, interactions of NOACs with CYP3A4/P-gp inhibitors showed a marginal effect in reducing the thromboembolic events while the concurrent use of both inhibitors and inducers had no effect on the risk of thromboembolic events.

Sexual pharmacokinetic differences are attributable to multiple factors, such as drug distribution, hepatic clearance and renal clearance.^{29,30} Sexual dimorphisms in metabolic enzymes and transportation are critical factors affecting pharmacokinetics.^{30,31} The risk of a thromboembolic event was higher in male patients when an NOAC was concurrently used with a CYP3A4/P-gp inducer. A possible mechanism is that the expression of P-gp is higher in men.³² In the small intestine, enhanced P-gp expression increases the excretion of its substrates from epithelial cells to the bowel lumen. Such recirculation re-exposes the drugs to metabolic enzymes in the gut, thereby reducing their bioavailability.

Two retrospective cohort studies have reported interesting results regarding the NOAC DDIs contradicting the direct pharmacokinetic effects. In 2017, Chang et al. indicated that in patients with NVAF using an NOAC (dabigatran, rivaroxaban or apixaban), the concurrent use of a CYP3A4/P-gp

inducer, such as rifampin (adjusted rate ratio [ARR] 1.57; 95% CI 1.02–2.41) or phenytoin (ARR 1.94; 95% CI 1.59–2.36), significantly increased the likelihood of a bleeding event (intracranial haemorrhage or gastrointestinal bleeding). In contrast, the concurrent use of a CYP3A4/P-gp inhibitor, such as erythromycin or clarithromycin (ARR 0.60; 95% CI 0.48–0.75), significantly reduced the incidence of bleeding events.¹⁷ In 2020, Wang et al. used a similar research method to analyse the relationship of the use of NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) and antiepileptic drugs with bleeding events; their results also indicated that the concomitant use of phenytoin (ARR 2.50; 95% CI 2.13–2.93) significantly increased the occurrence of bleeding events.³³ We propose 2 reasons for such contradicting observations. First, these 2 studies did not exclude patients with impaired renal function. NOACs are excreted by the kidneys in different degrees (dabigatran: 80%; rivaroxaban: 35%; apixaban: 27%; and edoxaban: 50%).³⁴ Renal function impairment may negatively affect NOAC elimination, meaning that NOACs have a stronger effect and resulting in an increased incidence of bleeding events. Second, these 2 studies did not explicitly define the duration of overlap between NOAC and interacting drug use. The duration of overlap may not have been sufficiently long to produce a major DDI. In the present nested case-control study, we matched the time at risk

and ensured an overlap of at least 7 days; any interactions were thus substantial, and the findings reflected the association between NOACs and CYP3A4/P-gp modifiers in terms of the incidence of thromboembolic events. Moreover, this study covered all NOACs and considered all 3 possible combinations (NOAC plus CYP3A4/P-gp inhibitor or inducer alone or an inhibitor and inducer simultaneously). To ensure that NOACs were used continuously, meaning that achieving the maximal clinical benefit of the drug was reasonably likely and the coverage of exposed drugs before the index date was appropriate, we calculated the PDC by NOACs. In addition, because NOACs should be used with caution in patients with poor renal function, patients with AF and chronic kidney disease or end-stage renal disease were excluded from this study.

Dabigatran is a substrate of the efflux transporter P-gp but is not metabolised by CYP3A4.³⁵ Consequently, the influence of CYP3A4/P-gp inhibitors or inducers may vary between patients using dabigatran and those using other NOACs. Sensitivity analyses were conducted for each individual NOAC, but no statistical significance was observed among patients taking CYP3A4/P-gp inhibitors or inducers. It is worth noting that these subpopulation analyses may be inadequately powered due to the limited sample sizes.

This study has several limitations. First, this is a nested case-control study. The major disadvantage of nested case-control studies is that not all pertinent risk factors are likely to have been recorded. Second, some clinical and physical information of the participants, such as the results of liver and kidney function tests, is not included in the NHIRD claims data. Third, the statistical power of the analysis regarding the strong CYP3A4/P-gp inhibitors and inducers was limited by the sample size. Additional studies are warranted to determine the effect of strong enzyme modifiers on NOACs. In addition, the cohort consisted of primarily Asian people, and direct extrapolation to other ethnic groups may thus be inappropriate.

CONCLUSION

For patients with NVAf taking NOACs, the concurrent use of a CYP3A4/P-gp inducer increases the risk of a thromboembolic event.

Acknowledgment

The authors would like to thank the National Health Research Institutes of Taiwan for providing the NHIRD. This manuscript was edited by Wallace Academic Editing.

Data availability statement

Data cannot be shared for ethical/privacy reasons.

Competing interest

All authors declare that no competing interests exist.

Funding

This work was supported by grants from the New Taipei City Hospital (NTPC 111-001) and Wan Fang Hospital (111-wf-swf-05). The funders had no role in the study design, data collection, analysis, publication decision or manuscript preparation.

REFERENCES

1. Kornej J, Börschel CS, Benjamin EJ, et al. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. *Circ Res* 2020;127:4-20.
2. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation* 2019;139:e56-e528.
3. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42:373-498.
4. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-962.
5. Ramos-Lima MJM, Brasileiro IC, Lima TL, et al. Quality of life after stroke: impact of clinical and sociodemographic factors. *Clinics (Sao Paulo)* 2018;73:e418.
6. Krishnamurthi RV, Ikeda T, Feigin VL. Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017. *Neuroepidemiology* 2020;54:171-9.
7. Katan M, Luft A. Global Burden of Stroke. *Semin Neurol* 2018;38:208-11.
8. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-104.
9. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
10. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.
11. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.
12. Silverio A, Di Maio M, Prota C, et al. Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440281 patients. *Eur Heart J Cardiovasc Pharmacother* 2021;7:f20-f29.
13. Mujer MTP, Rai MP, Atti V, et al. An Update on the Reversal of Non-Vitamin K Antagonist Oral Anticoagulants. *Adv Hematol* 2020;2020:7636104.

14. Hellenbart EL, Faulkenberg KD, Finks SW. Evaluation of bleeding in patients receiving direct oral anticoagulants. *Vasc Health Risk Manag* 2017;13:325-42.
15. Wang Y, Singh S, Bajorek B. Old age, high risk medication, polypharmacy: a 'trilogy' of risks in older patients with atrial fibrillation. *Pharm Pract (Granada)* 2016;14:706.
16. Jaspers Focks J, Brouwer MA, Wojdyla DM, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. *BMJ* 2016;353:i2868.
17. Chang SH, Chou IJ, Yeh YH, 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.
18. Wiggins BS, Northup A, Johnson D, et al. Reduced Anticoagulant Effect of Dabigatran in a Patient Receiving Concomitant Phenytoin. *Pharmacotherapy* 2016;36:e5-7.
19. Vakkalagadda B, Frost C, Byon W, et al. Effect of Rifampin on the Pharmacokinetics of Apixaban, an Oral Direct Inhibitor of Factor Xa. *Am J Cardiovasc Drugs* 2016;16:119-27.
20. Stöllerberger C, Finsterer J. Interactions between non-vitamin K oral anticoagulants and antiepileptic drugs. *Epilepsy Res* 2016;126:98-101.
21. Molokhia M, Majeed A. Current and future perspectives on the management of polypharmacy. *BMC Fam Pract* 2017;18:70.
22. Cheng CL, Kao YH, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf* 2011;20:236-42.
23. Hsieh CY, Chen CH, Li CY, et al. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. *J Formos Med Assoc* 2015;114:254-9.
24. Loucks J, Zuckerman AD, Berni A, et al. Proportion of days covered as a measure of medication adherence. *Am J Health Syst Pharm* 2022;79:492-6.
25. Hachad H, Ragueneau-Majlessi I, Levy RH. A useful tool for drug interaction evaluation: The University of Washington Metabolism and Transport Drug Interaction Database. *Hum Genomics* 2010;5:61.
26. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation* 2019;140:e125-e151.
27. Perlman A, Goldstein R, Choshen Cohen L, et al. Effect of Enzyme-Inducing Antiseizure Medications on the Risk of Sub-Therapeutic Concentrations of Direct Oral Anticoagulants: A Retrospective Cohort Study. *CNS Drugs* 2021;35:305-16.
28. Testa S, Paoletti O, Legnani C, et al. Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants. *J Thromb Haemost* 2018;16:842-8.
29. Raccach BH, Perlman A, Zwas DR, et al. Gender Differences in Efficacy and Safety of Direct Oral Anticoagulants in Atrial Fibrillation: Systematic Review and Network Meta-analysis. *Ann Pharmacother* 2018;52:1135-42.
30. Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. *Eur Heart J Cardiovasc Pharmacother* 2017;3:163-82.
31. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* 2013;138:103-41.
32. Soldin OP, Chung SH, Mattison DR. Sex differences in drug disposition. *J Biomed Biotechnol* 2011;2011:187103.
33. Wang CL, Wu VC, Chang KH, et al. Assessing major bleeding risk in atrial fibrillation patients concurrently taking non-vitamin K antagonist oral anticoagulants and antiepileptic drugs. *Eur Heart J Cardiovasc Pharmacother* 2020;6:147-4.
34. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Europace* 2021;23:1612-76.
35. Ebner T, Wagner K, Wienen W. Dabigatran acylglucuronide, the major human metabolite of dabigatran: in vitro formation, stability, and pharmacological activity. *Drug Metab Dispos* 2010;38:1567-75.