Association of Potential Pharmacokinetic Drug Interaction of Non-vitamin K Antagonist Oral Anticoagulants (NOACs) in Atrial Fibrillation Patients and Risk of Major Bleeding

Pansu Chumworathayi[*1] , Chaiyasith Wongvipaporn[*1] ,
Tapakorn Ainganu , Warinthorn Tooltham , Weeraya Sonakoo , Verawan Uchaipichat[*2]

*1 Srinagarind Hospital , Faculty of Medicine , Khon Kaen University

[*2] Division of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Khon Kaen University.

Background and objective: Non-vitamin K antagonist oral anticoagulants (NOACs), including dabigatran etexilate, rivaroxaban, apixaban, and edoxaban, may have pharmacokinetic interactions with CYP3A4 inhibitors and/or P-glycoprotein competitors, leading to increased levels of NOACs and the risk of major bleeding. The objective was to assess the association between using NOACs with and without receiving concurrent medications with potential pharmacokinetic interactions through CYP3A4 inhibitors and/or P-glycoprotein competitors, and the risk of major bleeding in patients with non-valvular atrial fibrillation.

Methods: This retrospective cohort study utilized data from the information database at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. The subjects were patients with nonvalvular atrial fibrillation who have prescribed a NOAC during January 1st, 2016, to August 31st, 2023. The primary outcome was major bleeding, defined as hospitalization or emergency department visits with a first diagnosis of intracranial bleeding, gastrointestinal bleeding, or bleeding at other sites. Secondary outcomes included sub-outcomes of major bleeding and all-cause mortality. The association of the outcomes and concomitant use of NOACs and CY3A4 inhibitors and/or P-glycoprotein competitors were assessed using Poisson regression models and inverse probability of treatment weighting using propensity score calculated from the study's covariates.

Results: The study included 400 patients (mean age, 73.3 years; SD, 10.2), 227 males and 173 females. Among 400 patients, it contained 2,739 person-quarters receiving NOACs, dividing into apixaban 1,020 person-quarters (37.2%), rivaroxaban 871 person-quarters (31.8%), dabigatran etexilate 775 person- quarters (28.3%), and edoxaban 77 person- quarters (2.8%).Person-quarters of NOACs prescriptions with and without concurrent use of perpetrator medications were 1,529 (55.8%) and 1,210 (44.2%), respectively. The perpetrators included: atorvastatin (43.9%), digoxin (10.6%), amiodarone (5.2%), verapamil (1.7%), diltiazem (1.4%), naproxen (0.6%), ticagrelor (0.4%), tacrolimus (0.3%), and rifampicin (0.1%). Other perpetrators that were not given with NOACs included phenytoin, fluconazole, dronedarone, quinidine, HIV protease inhibitors (ritonavir, lopinavir, atazanavir, darunavir), other azoles (ketoconazole, itraconazole, posaconazole, or voriconazole), macrolide antibiotics (clarithromycin or erythromycin), and cyclosporine. Overall, major bleeding was observed 16 and 10 times in the group that received NOACs with and without perpetrator medications, respectively. The adjusted incidence rate ratio was 0.86 (95% CI, 0.46 - 1.60) with no statistically significant (p-value 0.634). Major bleeding was found in the group that received NOACs with atorvastatin, digoxin, and amiodarone with adjusted incidence rate ratios of 1.32 (95% CI, 0.55-3.18), 0.75 (95% CI, 0.10- 5.53), and 0.39 (95% CI, 0.02-2.92), respectively.

However, there was no statistically significant (p-value, 0.535, 0.778, and 0.362, respectively). According to secondary outcomes, intracranial bleeding was found 5 and 4 times in the group that received NOACs with and without perpetrator medications, respectively. The adjusted incidence rate ratio was 0.54 (95% CI, 0.14-2.18). Of interest, an adjusted incidence rate ratio was 0.93 (95% CI, 0.20-4.37) in the group that received NOACs with atorvastatin. Gastrointestinal bleeding was found 11 and 6 times in the group that received NOACs with and without perpetrators, with an adjusted incidence rate ratio of 1.01 (95% CI, 0.50-2.12). The adjusted incidence rate ratio were 1.51 (95% CI, 0.53-4.29), 0.61 (95% CI, 0.08-4.57), and 1.16 (95% CI, 0.15-8.62) for the group that received NOACs with atorvastatin, digoxin, and amiodarone, respectively. All-cause mortality was observed 6 and 2 times in the group that received NOACs with and without perpetrators, respectively, with an adjusted incidence rate ratio of 1.77 (95% CI, 0.75 – 4.22). The adjusted incidence rate ratios were 2.86 (95% CI, 0.57-14.29) and 1.45 (95% CI, 0.18-11.76) in the group that received NOACs with atorvastatin and digoxin, respectively. All of these results did not show a statistically significant (p-value >0.200). The other sites of bleeding were not found in this study. None of the bleeding incidence was observed in the group that received NOACs with verapamil, diltiazem, naproxen, ticagrelor, tacrolimus, and rifampicin.

Conclusion: In atrial fibrillation patients, CYP3A4 inhibitors and/or P-glycoprotein competitors which are commonly used with NOACs were atorvastatin, digoxin, and amiodarone. The incidence of major bleeding was higher in a group receiving CYP3A4 inhibitor and/or P-glycoprotein competitors. However, there was no statistically significant, possibly due to the small study population. Data from this study may be useful for conducting research in the future, and guiding for risk management, increased surveillance, and reducing the risk of major bleeding for patients receiving NOACs in the Srinagarind Hospital.

Keywords: non-vitamin K antagonist oral anticoagulants (NOACs), dabigatran, rivaroxaban, apixaban, edoxaban