Original Investigation

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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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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.

Abstract

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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