Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with non-valvular atrial fibrillation and prior gastrointestinal bleeding: a nationwide population-based study

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**Introduction**: Although non-vitamin K antagonist oral anticoagulant (NOAC) have superior efficacy and at least comparable safety to warfarin in patients with non-valvular atrial fibrillation (NVAF), there are limited evidences among the NVAF patients with history of gastrointestinal bleeding (GIB). We aimed to study the effectiveness and safety of NOAC among the NVAF patients and prior GIB.

**Methods**: Using the claims database of the Health Insurance Review and Assessment from January 2010 to April 2018, we constructed a retrospective cohort constituted of 42,048 oral-anticoagulant-naïve individuals (24,781 with NOAC and 17,267 with warfarin) with both AF and prior GIB. Primary outcomes were ischemic stroke, intracranial hemorrhage (ICH), GIB, major bleeding (ICH and GIB), and composite outcome. Also, the fatal events (mortality during hospitalization) for each outcome were evaluated to reflect severity. Cox proportional regression analysis was used to adjust covariates between the groups. Additional analysis was performed by the groups with warfarin and each NOAC category.

**Result**: There were total 1,426 (3.4%) ischemic stroke, 235 (0.6%) ICH, 825 (2.0%) GIB, 286 (0.7%), 1,053 (2.5%) major bleeding, and 2,386 (5.7%) composite outcomes during the follow-up. Fatal events for each outcome were 286/1,426 (20.1%), 77/825 (9.3%), 29/286 (10.1%), 106/1,053 (10.1%), and 390/2,386 (16.3%) for ischemic stroke, ICH, GIB, major bleeding, and composite outcome, respectively. During the follow-up, there were total 2,616/42,048 (6.2%) all-cause deaths. NOAC users were older and had a more female proportion, and had higher CHA2DS2-VASc scores compared to warfarin users, (mean age 72.9 vs. 69.7 years; female 44.9% vs. 40.5%; CHA2DS2-VASc score 4.3 vs. 4.0; all p-values <0.001). NOAC users showed lower risks than warfarin users in recurrent GIB, ischemic stroke, ICH, major bleeding, and composite outcome (adjusted hazard ratio (HR) [95% confidence interval (CI)] =0.81 [0.70-0.94]; 0.61 [0.54-0.69], 0.48 [0.36-0.65], 0.73 [0.64-0.83], and 0.66 [0.60-0.72], respectively, Figure). For fatal outcomes, NOAC was associated with lower risks of ischemic stroke, ICH, major bleeding, and composite outcome, whereas it had a comparable risk of GIB to warfarin. By NOAC categories, edoxaban was associated with the lowest risk for all the 5 clinical outcomes and also all-cause death; 0.34 [0.25-0.46], 0.40 [0.20-0.83], 0.64 [0.46-0.88], 0.58 [0.43-0.78], 0.43 [0.35-0.54], and 0.59 [0.50-0.71] for ischemic stroke, ICH, major bleeding, composite outcome, and all-cause death, respectively.
Conclusion: NOAC was associated with lower risks of recurrent GIB, ischemic stroke, ICH, and fatal events in patients with AF and prior GIB.