Non-vitamin K antagonist oral anticoagulants versus warfarin in Asian patients with non-valvular atrial fibrillation and a history of intracranial hemorrhage: a nationwide cohort study

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**Introduction**: It has been demonstrated that oral anticoagulation therapy based on the warfarin in patients with non-valvular atrial fibrillation (AF) and a history of intracranial hemorrhage (ICH) might be associated with better net clinical benefit than no treatment. However, there was limited data for effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in these patients, especially in Asian population. We aimed to compare the effectiveness and safety of NOACs to warfarin in a large-scale nationwide Asian population with AF and a history of ICH.

**Methods**: Using the Korean Health Insurance Review and Assessment database from January 2010 to April 2018, we identified OAC naïve non-valvular AF patients with a prior history of ICH. For the comparison, warfarin and NOAC groups were balanced using inverse probability of treatment weighting method (IPTW). The primary outcomes were ischemic stroke, ICH, composite outcome (ischemic stroke + ICH). The secondary outcomes were fatal ischemic stroke, fatal ICH, death from composite outcome, and all-cause death.

**Result**: Among 5,712 AF patients with prior ICH, 2,434 were treated with warfarin and 3,278 were treated with NOAC (1,235 with rivaroxaban, 637 with dabigatran, 919 with apixaban, and 487 with edoxaban). Baseline characteristics were well-balanced after IPTW (mean age 72.5 years, 57.2% men, and mean CHA2DS2-VASc score 4.0). Compared to warfarin, NOAC was associated with lower risks of ischemic stroke (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.61-0.96), ICH (HR 0.66, 95% CI 0.47-0.92), and composite outcome (HR 0.73, 95% CI 0.60-0.88) (Figure). NOAC was associated with lower risks of fatal stroke (HR 0.54, 95% CI 0.32-0.89), death from composite outcome (HR 0.53, 95% CI 0.34-0.81) and all-caused death (HR 0.83, 95% CI 0.69-0.99) than warfarin. Also, NOAC showed nonsignificant trends towards to reduce fatal ICH compared to warfarin (HR 0.47, 95% CI 0.20-1.03). Among NOACs, apixaban showed a significant and the greatest risk reduction for ICH compared to warfarin (HR 0.48, 95% CI 0.25-0.84).

**Conclusion**: NOAC use was associated with a significant lower risk of ICH and ischemic stroke compared to warfarin. The results might be useful guidance for selecting oral anticoagulants in patients with non-valvular AF and a prior history of ICH.