Label adherence of direct oral anticoagulants dosing and clinical outcomes in patients with atrial fibrillation

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Introduction: Dose adjustment of non-vitamin K antagonist oral anticoagulants (NOACs) is indicated in some patients with atrial fibrillation (AF), based on selected patient factors or concomitant medications. We assessed the frequency of label adherence of NOAC dosing among AF patients and the associations between off-label NOAC dosing and clinical outcomes.

Methods: We evaluated 53,649 AF patients treated with a NOAC using Korean National Health Insurance Service database during the period from 2013 to 2016. NOAC doses were classified as either underdosed or overdosed, consistent with Korea Food and Drug Administration labeling. Cox proportional hazards regression was performed to investigate the effectiveness and safety outcomes including stroke or systemic embolism, major bleeding, and all-cause mortality.

Result: Overall, 16,757 NOAC-treated patients (31.2%) were underdosed, 4,492 were overdosed (8.4%), and 32,400 (60.4%) were dosed appropriately according to drug labeling. Compared with patients with label adherence, those who were underdosed or overdosed were older (71±8 and 75±7 years of age vs. 70±9 years of age, respectively; p<0.001) and had higher CHA2DS2-VASc scores (4.6±1.7 and 5.3±1.7 vs. 4.5±1.8, respectively; p<0.001). NOAC overdosing was associated with increased risk for stroke or systemic embolism (5.76 vs. 4.03 events/100 patient-years, p<0.001), major bleeding (4.77 vs. 2.94 events/100 patient-years, p<0.001), and all-cause mortality (5.43 vs. 3.05 events/100 patient-years, p<0.001) compared with label-adherent use.

Conclusion: In real-world practice, a significant proportion (almost 2 in 5) of AF patients received NOAC doses inconsistent with drug labeling. NOAC overdosing is associated with worse clinical outcomes in Asian patients with AF.