Letter by Kawada Regarding Article, “Dabigatran Versus Warfarin: Effects on Ischemic and Hemorrhagic Strokes and Bleeding in Asians and Non-Asians With Atrial Fibrillation”

To the Editor:

Hori et al. conducted a randomized study of long-term anticoagulation therapy for Asian and non-Asian patients with atrial fibrillation by using 2 doses of dabigatran etexilate (DE) versus warfarin on several types of stroke and bleeding rates. They handled 2782 Asian patients and 15,331 non-Asian patients, and Cox regression model was applied for risk assessment.1

Hemorrhagic stroke was significantly reduced by using DE 110 mg and DE 150 mg versus warfarin in Asian patients, presenting hazard ratios (95% confidence interval) of 0.15 (0.03–0.66) and 0.22 (0.06–0.77), respectively. In non-Asian patients, hazard ratios (95% confidence interval) of DE 110 mg and DE 150 mg versus warfarin were 0.37 (0.19–0.72) and 0.28 (0.13–0.58), respectively. In contrast, there was an ethnic difference on the risk of ischemic stroke when DE 150 mg was used.

In cases of major bleeding rates, hazard ratios (95% confidence interval) of DE 110 mg and DE 150 mg versus warfarin in Asian patients were 0.57 (0.39–0.85) and 0.57 (0.38–0.84), respectively. In non-Asian patients, hazard ratio (95% confidence interval) of DE 110 mg versus warfarin was 0.85 (0.73–0.99), and there was no significant reduction when DE 150 mg was applied. In cases of intracranial hemorrhage rates, there was no ethnic difference on the significant reduction effect of DE 110 mg and DE 150 mg versus warfarin. Although the authors concluded that hemorrhagic stroke was significantly reduced by DE in both Asians and non-Asians, I have a query on their statistical application to subgroup analysis.

Hori et al. selected treatment, region, treatment-by-region interaction, and age as independent variables for Cox regression analysis. I understand that there was no significant interaction on efficacy outcome, but the risk of bleeding should be handled with caution. When significant interaction was observed, the analysis should be conducted in Asian patients and non-Asian patients, separately. Concato et al. and Peduzzi et al. reported that the number of events per independent variable in Cox regression analysis should be ≥10 to keep statistical power. Hori et al. handled 2 doses of DE separately versus warfarin separately, and the number of gastrointestinal major bleeding in Asian patients with DE 150 mg versus warfarin was 41. According to the proposal by Peduzzi et al., the number of independent variables was limited within 4. Although the adjustments by some traditional risk factors for stroke and bleeding were not required for a randomized study, more events would be effective for stable risk assessment.

Also, ethnic difference should be more precisely evaluated. I suppose that there is an ethnic difference within 10 Asian countries and also within 34 non-Asian countries. I recommend the authors to continue their 2.5-year follow-up study to increase the number of events for Asian patients. Their study limitations can be resolved by following the prognosis of baseline data.

Disclosures

None.

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References

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