Gastrointestinal Bleeding in Japanese Patients With Atrial Fibrillation

— Non-Critical Site Bleeding, But With Poor Prognosis —

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Prevention of intracranial hemorrhage has gained marked attention in the management of patients with atrial fibrillation (AF) using oral anticoagulants (OACs). Direct OAC (DOACs) have shown efficacy at least equivalent to that of warfarin, with a lower major-bleeding incidence and likelihood of food and drug interactions, and have become the preferred thromboembolic therapy.¹ DOACs' advantage mainly lies in their association with lower intracranial-hemorrhage incidence, but a significant increase in the gastrointestinal (GI)-bleeding incidence has been reported.¹ In Asian populations, DOACs notably reduce intracranial-hemorrhage incidence, and the GI-

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bleeding incidence is not significantly different from that with warfarin use.² Therefore, it is assumed that DOACs' advantage is greater in Asian populations. However, the incidence and prognosis of GI bleeding in Japanese patients with AF using OACs remain uncertain.

In this issue of the Journal, Murata and colleagues³ report their subanalysis of the SAKURA AF Registry, including 3,237 patients taking OACs. The GI-bleeding incidence was 2.1% and comparable between warfarin and

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DOAC use. They found that renal impairment and anemia were GI-bleeding predictors and that GI bleeding was associated with poor prognosis.

The GI-bleeding incidence in the Japanese AF population using OACs has been reported, but such reports have been based on relatively small samples. In a subanalysis of the RE-LY trial, the annual rates of GI major bleeding for dabigatran 220 and 300mg and warfarin groups of Japanese patients were 2.11, 0.67, and 0.67, respectively (Figure).⁴ In the J-ROCKET AF study, the annual rates of non-critical site bleeding (GI bleeding, epistaxis, hematoma, hematuria, skin, and others) were 1.51% with rivaroxaban and 1.55% with warfarin.⁵ The SAKURA AF Registry included a larger number of patients, and the results were in line with those previously reported. The GI-bleeding annual rates (including minor bleeding) in patients using DOACs and warfarin were 0.67% and 0.75%, respectively.

Among the different DOACs, apixaban has the lowest GI-bleeding risk than either dabigatran or rivaroxaban.⁶ In the SAKURA AF Registry, patients using apixaban were significantly older and had more comorbidities than those using dabigatran or rivaroxaban. The data suggest that physicians should consider DOAC-profile differences and cautiously select apixaban in elderly patients aiming to reduce GI-bleeding events. Nevertheless, the GI-bleeding annual rate in patients using apixaban was 1.10% and modestly higher than that in patients using other DOACs or warfarin. This observation may be partially explained by the increased rate of GI bleeding in elderly patients (≥ 75 years old) using DOACs.^{7,8} In fact, the same research group reported that major bleeding was significantly more frequent in elderly than in non-elderly (< 75 years old) patients in the SAKURA AF Registry.⁹ Therefore, further investigation is warranted to explore the incidence of DOAC-use-associated GI bleeding in elderly Japanese patients.

Renal impairment increases both thromboembolism and major-bleeding incidence. Despite established evidence that DOACs are safe and efficacious in real-world settings, OACs continue to be underused in AF, partly because of perceived bleeding risk in patients with renal impairment. In the SAKURA AF Registry, fewer GI-bleeding events were noted among the patients (22%) who were administered under-dose than standard-dose DOACs. Although a previous subanalysis from the same group described that thromboembolic events were similar between under-dose and standard dose DOAC groups,¹⁰ the result should be cautiously interpreted. The XAPASS study showed that any bleeding was lower in patients who received under-dose rivaroxaban, whereas major bleeding was comparable between groups.¹¹ More importantly, the incidence of stroke/non-central nervous system embolism and myocardial infarction was higher in the under-dose group. Different DOAC profiles may affect the outcomes of thromboembolism and bleeding, but concrete evidence is lacking to justify the prescription of off-label low-dose DOACs.

GI bleeding is associated with significant morbidity and poor prognosis. In their article,³ the authors describe that GI bleeding predicted poor prognosis in Japanese patients with AF. Interestingly, only 25% of patients died of GI bleeding, and no thromboembolic events were observed, signifying that GI bleeding reflected poor patient condition rather than being a direct cause of death for most patients. However, it is uncertain whether the study results can be generalized to elderly populations at higher risk of throm-

boembolism and bleeding.⁹ A large non-Asian population-based study, including more elderly patients (78.3 ± 9.3 years), reported a higher mortality rate after GI bleeding.¹² At 2 years, 27% of patients required cessation of thromboembolic therapy, and the cumulative incidence of thromboembolism, major bleeding, and recurrent GI bleeding was 12%, 17.7%, and 12.1%, respectively. Another large population-based study (age 79.5 ± 7.3 years) reported that the 5-year risk of death among patients with recent GI-bleeding events was higher than that among patients with recent stroke.¹³ Details of OAC prescription at the time of the events in both these studies are unknown, but the potential for a high mortality rate in patients with recent GI bleeding should be considered when making shared decisions with elderly patients. Importantly, stroke prevention surpasses the bleeding risk even in elderly patients.⁹ However, absolute and relative risks of thromboembolism, intracranial hemorrhage, and major bleeding should be taken into account and individualized anticoagulant therapy should be considered in elderly patients with a previous GI-bleeding event. Whether DOACs and warfarin carry equivalent risks for GI bleeding and its prognosis in elderly Japanese patients with AF remains unclear.

In conclusion, the SAKURA AF Registry highlighted the importance of GI bleeding in real-world practice. Although GI bleeding is defined as non-critical site bleeding,¹⁴ it is associated with the death of Japanese patients with AF. Ethnic differences, especially regarding the bleeding risk with DOAC use in elderly patients (≥ 75 years old), should be further investigated.

Disclosures

None.

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