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REVIEW

Current Real-World Status of Oral Anticoagulant Management in Japanese Patients

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Anticoagulant therapy is a drug therapy that inhibits the formation of blood clots. Although anticoagulants are effective in preventing thromboembolism, they also carry the risk of bleeding, so they must be managed carefully, taking both efficacy and safety into account. Evidence regarding the effectiveness and safety of each anticoagulant has already accumulated through many large clinical trials and post-marketing surveillance. However, when making decisions in clinical practice, it is necessary to always take into consideration differences in patient populations between clinical trials and actual clinical practice, as well as differences in historical background. (For example, there are differences in antiplatelet drugs and coronary artery interventions that were mainly used in each era.) In this review we discuss the effectiveness and safety of currently used anticoagulants, focusing on different patient backgrounds and points to keep in mind regarding their proper use, based on the latest reports in Asian populations, especially Japanese people, over the past 1–2 years.

Key Words: Anticoagulant; Atrial fibrillation; Venous thromboembolism

Although anticoagulants are effective in preventing thromboembolism, they also carry the risk of bleeding, so they must be managed carefully, taking both efficacy and safety into account. In this review we discuss the effectiveness and safety of currently used anticoagulants, focusing on different patient backgrounds and points to keep in mind regarding their proper use, based on the latest reports in Asian populations, especially Japanese people, over the past 1–2 years.

Non-Valvular Atrial Fibrillation

Recently, non-vitamin K oral anticoagulants (NOACs) have been shown to be effective and safe in preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF).[1] Although the effectiveness and safety of NOACs compared with warfarin are supported by data primarily from Western countries,[2] there has been considerable debate regarding the efficacy and safety of NOACs in Asian populations, where the average body weight of patients with atrial fibrillation (AF) is lower than that of patients from non-Asian populations. However, over the years, the desired efficacy and safety of NOACs has been established in Asian countries, including Japan.[3]

For example, a recent international large-scale observational study on edoxaban for NVAF patients in 4 Asian countries/regions demonstrated that most Asian patients with NVAF were prescribed recommended edoxaban dosing in routine care settings (70.9% of a total of 3,359 patients).[4] In addition to the high adherence to the recommended dose of edoxaban, the event rates for ischemic stroke and major bleeding remained low (<1.5%) over the 1-year follow-up period.[4]

Elderly Populations

The risk of cerebral infarction in very elderly patients with AF is extremely high if they receive insufficient anticoagulant therapy, and anticoagulant therapy should be considered first even if they have cognitive impairment, frailty, or renal dysfunction.[5]

The All Nippon AF In Elderly (ANAFIE) Registry, a prospective multicenter observational study in Japan, provided real-world insights into NVAF in >30,000 elderly (age ≥75 years) Japanese patients.[6] Over a 2-year follow-up period, NOACs yielded a numerically lower event incidence vs. warfarin in all age groups and for majority of endpoints, except major bleeding in patients aged ≥90 years.[6] Although NOACs, compared with warfarin, offered potential benefits for stroke prevention, they had limited efficacy in reducing major bleeding among those aged ≥90 years, indicating a potential benefit of very-low-dose NOACs for this demographic.[6] In another study looking at longer-term results, subgroup analysis of the Hokuriku-Plus AF Registry with

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a median follow-up of 5.0 years revealed that the efficacy and safety of NOACs were more pronounced in elderly (age ≥75 years) NVAF patients compared with non-elderly NVAF patients considering the competing risk of death.[7] As suggested by these recent data, NOACs may be a preferable choice for the treatment of Japanese elderly patients with NVAF.

Drug Monitoring

In clinical practice, anticoagulation therapy should be discontinued if a bleeding event occurs, especially in cases of life-threatening bleeding. Anticoagulant therapy should be restarted after the bleeding event subsides. Unlike warfarin, NOACs have the advantage of not requiring frequent drug monitoring and have preferable efficacy and safety; however, adjusting the dose according to body weight or renal function does not necessarily provide the optimal outcome in every individual case. Although in actual clinical practice the use of reduced off-label NOAC doses is a problem, there is no established method for the drug monitoring of NOACs as there is for warfarin, a vitamin K antagonist. Despite a limited sample size, a single-center study suggested that monitoring plasma concentrations of NOACs in patients with NVAF using anti-Factor Xa chromogenic assays may allow dose adjustments to reduce bleeding risk.[8]

Nutrition Management

Although NOACs are now widely accepted as an alternative to conventional warfarin for the treatment of NVAF and venous thromboembolism (VTE), there are still many cases where warfarin is required, including for patients supported with a left ventricular assist device (LVAD). It is widely known that the efficacy of warfarin, a vitamin K antagonist, is strongly influenced by dietary vitamin K intake. A study conducted by the National Cerebral and Cardiovascular Center showed that during the 2018 Osaka Earthquake, there was a marked change in the international normalized ratio of prothrombin time (PT-INR) of patients with an LVAD despite their consumption of only 1–2 days of emergency food.[9] The authors of that study reiterated the importance of carefully monitoring PT-INR and assessing vitamin K content to prevent complications in those on warfarin, including LVAD patients, in Japan, a disaster-prone country.

Combination of Antiplatelet and Anticoagulant Drugs

It is well-established that antithrombotic therapy after percutaneous coronary intervention (PCI) plays a crucial role in the secondary prevention of cardiovascular disease (CVD).[10] However, there is concern about the potentially higher risk of bleeding among patients with CVD under antithrombotic therapy.[11] In addition, there are changes in PCI strategies and anticoagulant drugs used over time, which must be considered when making clinical decisions.

A large multicenter survey on the current status of antithrombotic therapy for Japanese NVAF patients undergoing PCI from 2014 to 2022 provides very specific historical information regarding anticoagulation in Japan.[12] Briefly, the use of drug-eluting stents and NOACs has become widespread, and triple therapy within 1 month has become mainstream for both acute and chronic coronary syndrome patients with NVAF. Starting in 2020, the most common time for discontinuation of antiplatelet combination therapy and to transition to NOAC monotherapy was 1 year after PCI.[12] In addition, post hoc analysis of the PENDULUM study suggested that a WOEST-like regimen with prasugrel may reduce bleeding, without increasing major adverse cardiovascular events, in Japanese patients with NVAF and high bleeding risk undergoing PCI.[13] It is expected that an ongoing multicenter prospective study in Japan (the REWRAPS trial) will provide evidence of the efficacy and safety of NOAC monotherapy >1 year after PCI (vs. warfarin monotherapy) in real-world Japanese patients with NVAF and chronic kidney disease.[14]

As a note of caution, there is not entirely enough evidence regarding sex-specific recommendations for the treatment of women with NVAF undergoing PCI, because women are often underrepresented in clinical trials in this setting.[15] Recent findings regarding sex differences in bleeding complications after PCI do not provide sufficient evidence to recommend specific treatments for women.[15] Further research is needed to address this gap and recommend optimal antithrombotic therapy for women after PCI.[15]

Venous Thromboembolism

Recently, clinical trials evaluating the effectiveness and safety of DOACs for VTE therapy have demonstrated that DOACs are non-inferior to standard heparin/vitamin K antagonist regimens.[16–19] For example, a recent retrospective analysis in Japan revealed that the effectiveness of deep vein thrombosis treatment using rivaroxaban monotherapy, as evaluated by a quantitative ultrasound thrombosis score over a period of 3 months from onset, was equivalent to traditional heparin/vitamin K antagonist combination therapy.[20] Another single-center retrospective study in Japan demonstrated that the safety of the 3 NOACs (edoxaban, rivaroxaban, and apixaban) for Japanese patients with VTE did not differ significantly in clinical settings, despite differences in patient demographics.[21]

The J'xactly Study is a well-known study that demonstrated the efficacy and safety of rivaroxaban in clinical practice in Japan for patients with deep vein thrombosis and pulmonary embolism.[22] In recent years, various subgroup analyses of the J'xactly Study have provided evidence of the efficacy and safety of rivaroxaban. One subanalysis, which focused on the duration of intensive rivaroxaban therapy during the acute phase of VTE, validated that the standard initial intensive rivaroxaban treatment (17–24 days) was relatively safe and effective.[23] In another subanalysis focusing on the presence of triggers for the development of VTE, patients without VTE triggers were relatively younger, less likely to be female, and had a higher body weight.[24] In addition, the incidence of symptomatic VTE recurrence was significantly higher in the group without triggers, suggesting caution in discontinuing NOACs during the chronic phase of VTE.[24] An analysis of the group of patients who required discontinuation of anticoagulant therapy during the clinical course showed that patients with cancer had a higher incidence of major bleeding, whereas the long-term recurrence rate of VTE was higher in patients without neither cancers nor VTE triggers.[25]

Conclusions

Considerable evidence has been presented regarding the effectiveness and safety of anticoagulants. However, there are many concerns when applying past literature to actual clinical practice, such as differences between Japan and other countries and the fact that the antiplatelet drugs used concomitantly have changed over time. In this review, we provide an overview of the effectiveness and safety of anticoagulants, including findings based on the latest actual data from Japanese patients. These findings have been suggested that novel anticoagulants have relatively preferable efficacy and safety in Asian populations, including Japan.

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Disclosures / IRB Information / Data Availability

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