JACC: ASIA VOL. 2, NO. 6, 2022

EDITORIAL COMMENT

Anticoagulation for Atrial Fibrillation in the Very Elderly

Make or Break?*

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The prevalence of atrial fibrillation (AF) is increasing worldwide. Population aging is prominent in high-income countries, which also promotes an increase in patients with AF. AF increases cardiovascular risks, including cerebral infarction, and poses a high burden on the health care economy. Therefore, reducing the cerebro-/cardiovascular risk in patients with AF has become crucial. Anticoagulation is an established therapy for reducing the risk of stroke in patients with AF. However, because the risk of major bleeding is high in elderly patients, active anticoagulation increases the risk of cerebral and systemic hemorrhage. Therefore, a solution to the opposing problem of reducing the risk of stroke and hemorrhage is required.

Results of the ELDERCARE-AF (Edoxaban Low-Dose for Elder Care in AF Patients) study[1] in 2020 indicated that the oral administration of ultra-low-dose edoxaban (15 mg/day) reduced ischemic stroke incidence without significantly increasing bleeding compared with placebo in a group of very elderly Japanese patients with high bleeding risk.

East Asians, including the Japanese, have a higher bleeding risk than Caucasians do.[2] It has been 10 years since the introduction of direct oral anticoagulants (DOACs); however, scarce data exist regarding the kind of anticoagulation performed in daily clinical settings and outcomes in the elderly and high bleeding risk group. Notably, these elderly patients with a high bleeding risk were not the main population in most randomized trials.

In this issue of *JACC: Asia*, Okumura et al[3] report real-world data on anticoagulation in very elderly patients with non-valvular atrial fibrillation in Japan. The investigators performed a subanalysis of data from the ANAFIE (All Nippon AF in the Elderly) registry. The ANAFIE registry was established to clarify the anticoagulant therapy and clinical outcomes of elderly patients with nonvalvular AF in real-world clinical practice in Japan.[4] This study was a prospective multicenter registry. Based on the results of ELDERCARE-AF, the investigators divided the patients in the ANAFIE registry into an ELDERCARE-AF-like group (high bleeding risk group) and others (non-high-risk group). Focusing on the high-risk bleeding group, they investigated the therapeutic efficacy and safety of anticoagulant therapy.

As shown in **Figure 1**, 89% of the patients in the high-risk group were clinically anticoagulated despite the high bleeding risk, including 30.1% with warfarin and 58.9% with DOACs. In the non-high-risk group, 93.4% of patients received anticoagulant therapy, of which 24.2% were on warfarin and 69.1% were on DOACs. In the high-risk group, 71.5% of the patients received on-label reduced doses. Underdose, or reduction not meeting the dose-reduction criteria, was 7.3% in the high-risk group and 19.1% in the non-high-risk group.

The high-risk group had significantly higher rates of primary endpoints, including stroke/systemic embolism and major bleeding, than the non-high-risk group did. Analysis of the high-risk group

*Editorials published in the *JACC: Asia* reflect the views of the authors and do not necessarily represent the views of *JACC: Asia* or the American College of Cardiology.

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Toru Suzuki, MD, PhD, served as Guest Editor-in-Chief for this paper.

The author attests he is in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2022.08.012

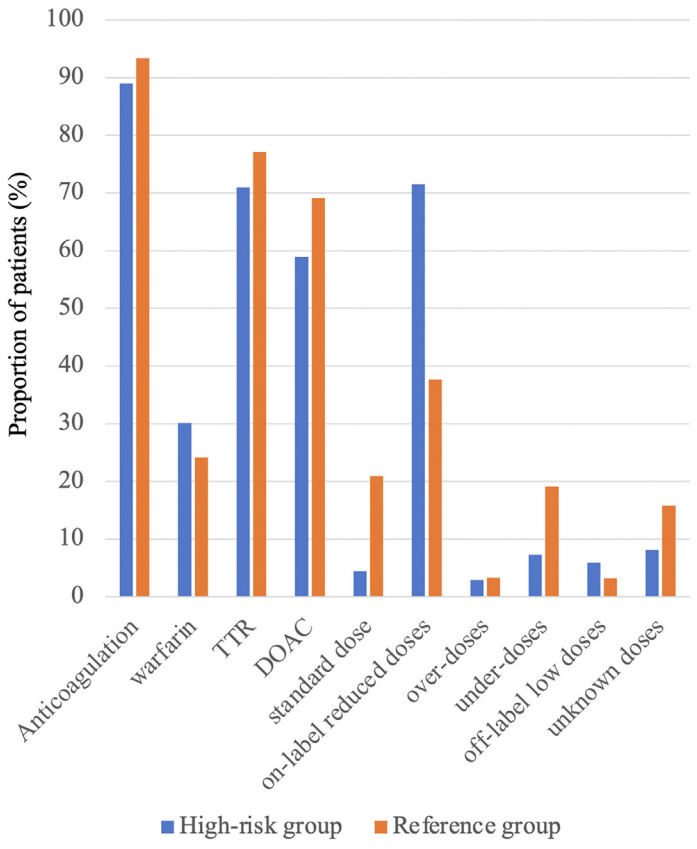
indicated that DOACs significantly reduced the incidence of stroke/systemic embolism and intracranial bleeding compared with warfarin and no anticoagulant treatment. Occurrence of major bleeding was suppressed by DOACs compared with warfarin; however, there was no difference in the incidence of major bleeding between patients under DOACs and without anticoagulant treatment. There was no difference in the occurrence of all bleeding events between the DOACs and warfarin, although the event incidence was higher in the DOACs group than in the no anticoagulant treatment group. There was no significant difference in the incidence of gastrointestinal bleeding between DOACs, warfarin, and no anticoagulation. In terms of net clinical outcomes, DOACs were significantly better than the other 2 strategies. Among the baseline variables for patients in the high-risk group, those with a history of major bleeding, severe hepatic impairment, and a history of falls within 1 year were at an increased risk of major bleeding.

Among the patients enrolled in this study, anticoagulation was performed in approximately 90% of the patients who were ELDERCARE-AF-like and very elderly and had a high risk of bleeding. Furthermore, the fact that the overdosage was only about 3% probably reflects that a careful risk assessment was performed by the clinicians.

Based on the results of the ELDERCARE-AF study, edoxaban 15 mg/day has already been approved in Japan. However, this "ultra-low-dose edoxaban" was included in the off-label low-dose category at the time of the present registry. Interestingly, the off-label low-dose DOAC group showed a lower incidence of both stroke and major bleeding at 2% compared to the on-label DOAC group (however, detailed data were not provided in the paper[3]). In the future, it will be necessary to compare the efficacy and safety between on-label reduced doses (30 mg/day for edoxaban) and lower doses (15 mg/day). Furthermore, ultra-low doses of other DOACs should also be assessed. Besides, this study reflects real-world clinical data on anticoagulant therapy in Japanese patients only; therefore, data from other East Asians who may have similar bleeding risks are also desirable.

Taken together, the results of the present study[3] suggest that DOACs should be recommended as anticoagulants for nonvalvular AF according to the current guidelines, even in very elderly patients with high bleeding risk.[5,6] More comparisons are needed in the future on the efficacy and safety of normally reduced and ultra-low-doses of DOACs.

FIGURE 1 Reported Proportion of Anticoagulation



The reported proportions of patients according to anticoagulation strategies are shown. See Okumura et al[3] for details. DOAC = direct oral anticoagulant; TTR = time in therapeutic range.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

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JACC: ASIA, VOL. 2, NO. 6, 2022
NOVEMBER 2022:734–736

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KEY WORDS anticoagulants, atrial fibrillation, high risk, outcomes, very elderly