Oral Anticoagulants in Very Elderly Nonvalvular Atrial Fibrillation Patients With High Bleeding Risks

ANAFIE Registry

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ABSTRACT

BACKGROUND Data on the effectiveness and safety of oral anticoagulant (OAC) agents in very elderly nonvalvular atrial fibrillation patients with high bleeding risk are lacking.

OBJECTIVES This study examined 2-year outcomes and effects of OAC agents among these patients using the ANAFIE (All Nippon Atrial Fibrillation in the Elderly) registry (N = 32,275) data.

METHODS Patients were classified into high-risk (age: ≥80 years; CHADS2 score: ≥2; and presence of ≥1 bleeding risk factor: creatinine clearance of 15-30 mL/minute, prior bleeding at critical sites, body weight of ≤45 kg, or continuous antiplatelet use) and reference groups.

RESULTS In the high-risk (n = 7,104) and reference (n = 25,171) group patients, 89.0% and 93.4%, respectively, used OAC agents. Of these, respectively, 30.1% and 24.2% used warfarin, and 58.9% and 69.1% used direct-acting OAC (DOAC) agents. Compared with the reference group, the high-risk group had higher incidences of stroke/systemic embolism, major bleeding, intracranial hemorrhage, gastrointestinal bleeding, cardiovascular events, and all-cause death. In the high-risk group, DOAC agent use vs nonuse of OAC agents was associated with reduced incidences of stroke/systemic embolism (HR: 0.53; 95% CI: 0.36-0.79) and all-cause death (HR: 0.65; 95% CI: 0.52-0.81) but not with major bleeding (HR: 1.09; 95% CI: 0.63-1.89). DOAC agents were superior to warfarin in effectiveness and safety. For high-risk patients, history of major bleeding, severe liver dysfunction, and falls within 1 year were independent risk factors for major bleeding.

CONCLUSIONS High-risk elderly nonvalvular atrial fibrillation patients had higher event incidences. DOAC agents were associated with reduced risk of stroke/systemic embolism and all-cause death vs nonuse of OAC agents or warfarin.

(Prospective Observational Study in Late-Stage Elderly Patients With Nonvalvular Atrial Fibrillation [ANAFIE registry]; UMIN000024006) (JACC: Asia 2022;2:720–733) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Worldwide, atrial fibrillation (AF) is the most common sustained arrhythmia affecting adults, with more than 33 million affected individuals, and is considered a well-established and growing global epidemic. AF is associated with high morbidity and mortality among those affected. Because aging is the most important risk factor for developing AF, AF-related complications, such as cardiac dysfunction and stroke, and their sequelae are expected to increase.

Therapeutic and management strategies and stroke prevention are evolving and improving. Based on the results of large-scale clinical trials, various guidelines recommend administering oral anticoagulant (OAC) agents, especially direct-acting OAC (DOAC) agents, to prevent stroke in patients with AF, including elderly patients. It is, however, necessary to rigorously evaluate the current status of OAC agent use and outcomes among very elderly patients, who are generally excluded from most clinical trials. Additionally, treating very elderly patients with AF poses a considerable challenge, not only because of the aging process and its consequences but because of comorbidities, associated complications, and increased risk of bleeding.

The recent ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial showed that once-daily, very-low-dose edoxaban (15 mg) was superior to placebo in reducing stroke/systemic embolism (SE) in AF patients aged ≥80 years who were at high risk of bleeding and possibly ineligible for standard OAC therapy, and nonsignificantly increased major bleeding. Nevertheless, there is insufficient real-world evidence of the effectiveness and safety of OAC agents in nonvalvular AF (NVAF) patients who meet the ELDERCARE-AF eligibility criteria, that is, very elderly patients with high bleeding risk. The purposes of the present exploratory subanalysis of the ANAFIE (All Nippon AF in the Elderly) registry were to examine the prescription rate of OAC agents and the 2-year rate of events of interest among high-bleeding-risk patients and to describe the effect of OAC agents in this high-bleeding-risk population.

METHODS

STUDY DESIGN AND POPULATION. The ANAFIE registry was a large-scale, prospective, observational, real-world data study of more than 30,000 elderly (≥75 years of age) Japanese patients with NVAF, irrespective of OAC agent use, who were followed up for 2 years. The rationale, detailed study design, and methodology of the ANAFIE registry (UMIN000024006) have already been published. The study complied with the Declaration of Helsinki, the locally appointed ethics committees approved the research protocol, and participants provided informed consent.

For the present subanalysis, patients enrolled in the ANAFIE registry were classified into 2 groups, the ELDERCARE-AF-like high-risk group, defined as the patients who met the eligibility criteria for the ELDERCARE-AF trial (high-risk group), and the reference group, defined as the patients who did not meet the ELDERCARE-AF trial criteria. The criteria for inclusion in the high-risk group were age of ≥80 years; a CHADS2 score of ≥2; and the presence of ≥1 bleeding risk factor: creatinine clearance (CrCl) of 15-30 mL/min, except for patients with CrCl of <15 mL/min or undergoing dialysis; prior bleeding history at critical sites (ie, major upper or lower gastrointestinal bleeding or intracranial hemorrhage); body weight of ≤45 kg; and continuous single antiplatelet use (eg, aspirin, P2Y12 inhibitor, or other).

STUDY MEASURES. Events of interest evaluated in this analysis included the incidences of stroke/SE; major bleeding; all bleeding events (major bleeding, clinically relevant bleeding, and minor bleeding); intracranial hemorrhage; gastrointestinal bleeding; cardiovascular events including stroke/SE, myocardial infarction, heart failure, and cardiovascular death; all-cause death; and net clinical outcome (a composite of stroke/SE, major bleeding, and all-cause death) over the 2-year follow-up period. The events occurring in the high-risk group vs the reference group; the events occurring in the high-risk group.

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according to DOAC agent vs warfarin and DOAC agent vs nonuse of OAC agents; and the independent risk factors for stroke/SE, major bleeding, and intracranial hemorrhage were explored.

DOAC agent doses were defined as previously reported. Briefly, a standard dose was defined as the dose according to the label specified for patients not meeting the dose-reduction criteria; a reduced dose was the dose according to the label specified for patients who met the dose-reduction criteria; an overdose was the standard dose prescribed to patients who did not meet the dose-reduction criteria; and an off-label underdose was any dose lower than that specified by the label.

STATISTICAL ANALYSIS. The details of the statistical analysis and sample size calculations of the ANAFIE registry have been reported previously. Summary statistics were obtained for continuous variables, and a 2-sample Student’s t-test was used to calculate P values. Categorical variables were summarized using numbers and percentages, and P values were calculated using the chi-square test.

The Kaplan-Meier method was used to estimate the cumulative incidence rates of the events of interest at 2 years in the high-risk and reference groups. The log-rank test was used for between-group comparison.

For the comparison of incidence rates in the high-risk vs reference group, the Cox proportional hazards model was used, and HRs and 95% CIs were calculated. In this analysis, anticoagulant therapy was entered in the statistical model. To compare incidence rates between OAC agent use vs nonuse of OAC agents and to identify independent risk factors for stroke/SE, major bleeding, and intracranial hemorrhage, the variables possibly associated with the selection of anticoagulant therapy or incidence of outcomes were entered in the statistical model. All statistical analyses were performed using SAS version 9.4 or higher (SAS Institute).
RESULTS

PATIENTS. Figure 1 shows the patient disposition. Of the patients enrolled in the ANAFIE registry (N = 32,275), 22.0% (n = 7,104) were included in the high-risk group. The remaining 78.0% (n = 25,171) of patients made up the reference group.

Table 1 summarizes the main characteristics of patients in the high-risk and reference groups. Compared with the reference group, the high-risk group patients were older and had a higher prevalence of female sex, lower body weight, and lower CrCl. The prevalence of OAC agent use was slightly lower in the high-risk group (89.0%) than in the reference group (93.4%), and the rate of warfarin use was higher in the high-risk group (30.1%) than in the reference group (24.2%), whereas the rate of DOAC use was lower in the high-risk group (58.9%) than in the reference group (69.1%). In the high-risk group, 4.4% and 71.5% of patients received DOAC agents at standard doses and on-label reduced doses, respectively; in the reference group, 20.9% and 37.7% of patients were receiving DOAC agents at standard and on-label reduced doses, respectively. The other patients received underdoses (ie, reduced doses not meeting dose-reduction criteria; 7.3% in the high-risk group and 19.1% in the reference group), overdoses (ie, standard doses meeting the dose-reduction criteria; 2.9% in the high-risk group and 3.3% in the reference group), off-label (ie, nonapproved) low doses (5.9% in the high-risk group and 3.2% in the reference group), or unknown doses (8.1% in the high-risk group and 15.8% in the reference group). In patients receiving warfarin, the mean time in the therapeutic range (TTR) was lower in the high-risk group (71.0%) than in the reference group (77.1%); however, almost half of the patients evaluated had a TTR of ≥80% in both groups.

COMPARISON OF THE INCIDENCES OF MAJOR OUTCOMES BY GROUP. The 2-year incidence rates in the high-risk and reference groups are shown in Table 2. Stroke/SE occurred in 3.8% and 2.8%, respectively; major bleeding in 2.8% and 1.8%, respectively; intracranial hemorrhage in 1.7% and 1.3%, respectively; gastrointestinal bleeding in 4.4% and 3.3%, respectively; cardiovascular events in 17.5% and 8.7%, respectively; and all-cause death in 12.5% and 5.4%, respectively. The cumulative incidence rates of the main outcomes are presented in Table 2.

Among the high-risk group patients prescribed with DOAC agents, the 2-year incidences of stroke/SE, major bleeding, and all-cause mortality were 3.3%,
and 11.6%, respectively, in patients receiving on-label DOAC doses (n = 3,173; standard and reduced doses), whereas the incidences were 2.0%, 2.0%, and 11.5%, respectively, in those receiving inappropriately reduced off-label doses (n = 549; underdoses and off-label low doses) (data not shown).

**COMPARISON OF MAIN OUTCOMES ACCORDING TO ANTIMOAGULANT AGENT USE IN THE HIGH-RISK GROUP.** Table 3 shows the HRs for each event in the Cox proportional hazards model for the high-risk group according to OAC agent use (DOAC agent vs warfarin and vs nonuse of OAC agents) with univariate and multivariate analyses. Stroke/SE, major bleeding, intracranial hemorrhage, and net clinical outcome rates were significantly lower in the DOAC agent–treated group compared with the nonuse-of-OAC-agents group, whereas major bleeding rates did not significantly increase with DOAC agent treatment. The rate for all bleeding events (major bleeding, clinically relevant bleeding, and minor bleeding) was significantly higher in the DOAC agent–treated group than in the nonuse-of-OAC-agents group. Stroke/SE, major bleeding, intracranial hemorrhage, and net clinical outcome rates were significantly lower in the DOAC agent–treated group compared with the warfarin-treated patients, but no significant differences were observed for gastrointestinal bleeding, all-cause death, or cardiovascular death.

**RISK FACTORS ASSOCIATED WITH MAIN OUTCOMES IN THE HIGH-RISK GROUP.** Univariate and multivariate analyses of outcomes in the high-risk group according to baseline variables are shown in Table 4. Significant independent risk factors for stroke/SE were type of AF (long-standing AF), systolic blood pressure of ≥140 mm Hg, diabetes (glycated hemoglobin: ≥6.0%), cerebrovascular disease, and CrCl of ≥15 to <30 mL/min. Significant independent risk factors for major bleeding were a history of major bleeding events (major bleeding, clinically relevant bleeding, and minor bleeding) was significantly higher in the DOAC agent–treated group than in the nonuse-of-OAC-agents group. Stroke/SE, major bleeding, intracranial hemorrhage, and net clinical outcome rates were significantly lower in the DOAC agent–treated group compared with the warfarin-treated patients, but no significant differences were observed for gastrointestinal bleeding, all-cause death, or cardiovascular death.

**TABLE 2** Comparison of the Incidences of Major Outcomes by Group

| Outcome                         | Group          | Events (%) | Univariate Analysis | Multivariate Analysis |
|---------------------------------|----------------|------------|---------------------|-----------------------|
|                                 |                |            | HR (95% CI)         | P Value               | HR (95% CI)         | P Value               |
| Stroke/systemic embolism        | High risk      | 270 (3.8)  | 1.43 (1.24-1.64)    | <0.001                | 1.39 (1.21-1.60)    | <0.001                |
|                                 | Reference      | 700 (2.8)  | –                   | –                     | –                   | –                     |
| Stroke                          | High risk      | 260 (3.7)  | 1.41 (1.22-1.62)    | <0.001                | 1.37 (1.18-1.58)    | <0.001                |
|                                 | Reference      | 685 (2.7)  | –                   | –                     | –                   | –                     |
| Ischemic stroke                 | High risk      | 206 (2.9)  | 1.42 (1.21-1.67)    | <0.001                | 1.37 (1.16-1.61)    | <0.001                |
|                                 | Reference      | 537 (2.1)  | –                   | –                     | –                   | –                     |
| Hemorrhagic stroke              | High risk      | 51 (0.7)   | 1.25 (0.91-1.72)    | 0.162                 | 1.26 (0.91-1.73)    | 0.161                 |
|                                 | Reference      | 150 (0.6)  | –                   | –                     | –                   | –                     |
| Systemic embolism               | High risk      | 13 (0.2)   | 3.16 (1.51-6.65)    | 0.002                 | 2.96 (1.40-6.25)    | 0.004                 |
|                                 | Reference      | 15 (0.1)   | –                   | –                     | –                   | –                     |
| Major bleeding                  | High risk      | 198 (2.8)  | 1.64 (1.39-1.94)    | <0.001                | 1.61 (1.36-1.90)    | <0.001                |
|                                 | Reference      | 447 (1.8)  | –                   | –                     | –                   | –                     |
| Clinically relevant nonmajor bleeding | High risk | 181 (2.6)  | 1.35 (1.14-1.60)    | <0.001                | 1.36 (1.15-1.62)    | <0.001                |
|                                 | Reference      | 494 (2.0)  | –                   | –                     | –                   | –                     |
| Minor bleeding                  | High risk      | 344 (4.8)  | 1.23 (1.09-1.39)    | 0.001                 | 1.25 (1.10-1.41)    | <0.001                |
|                                 | Reference      | 1,036 (4.1)| –                   | –                     | –                   | –                     |
| All bleeding events ab          | High risk      | 675 (9.5)  | 1.33 (1.22-1.46)    | <0.001                | 1.34 (1.23-1.47)    | <0.001                |
|                                 | Reference      | 1,880 (7.5)| –                   | –                     | –                   | –                     |
| Intracranial hemorrhage         | High risk      | 122 (1.7)  | 1.36 (1.11-1.68)    | 0.004                 | 1.33 (1.08-1.64)    | 0.007                 |
|                                 | Reference      | 331 (1.3)  | –                   | –                     | –                   | –                     |
| Gastrointestinal bleeding       | High risk      | 309 (4.4)  | 1.38 (1.21-1.57)    | <0.001                | 1.39 (1.22-1.58)    | <0.001                |
|                                 | Reference      | 829 (3.3)  | –                   | –                     | –                   | –                     |
| Cardiovascular events           | High risk      | 1,240 (17.5)| 2.18 (2.03-2.34)   | <0.001                | 2.13 (1.98-2.28)    | <0.001                |
|                                 | Reference      | 2,177 (8.7)| –                   | –                     | –                   | –                     |
| All-cause death                 | High risk      | 886 (12.5) | 2.42 (2.23-2.64)    | <0.001                | 2.33 (2.14-2.54)    | <0.001                |
|                                 | Reference      | 1,355 (5.4)| –                   | –                     | –                   | –                     |
| Cardiovascular death            | High risk      | 303 (4.3)  | 3.20 (2.75-3.74)    | <0.001                | 3.04 (2.61-3.55)    | <0.001                |
|                                 | Reference      | 351 (1.4)  | –                   | –                     | –                   | –                     |
| Net clinical outcome            | High risk      | 1,148 (16.2)| 2.01 (1.88-2.16)   | <0.001                | 1.95 (1.82-2.10)    | <0.001                |
|                                 | Reference      | 2,124 (8.4)| –                   | –                     | –                   | –                     |

**a**High-risk group: n = 7,104; reference group: n = 25,171. **b**Anticoagulant agent use was included as an adjustment factor in the model. **c**All bleeding events (major bleeding, clinically relevant bleeding, and minor bleeding).
bleeding, severe liver dysfunction, and falls within 1 year. Significant independent risk factors of intracranial hemorrhage were severe liver dysfunction, fall within 1 year, and proton pump inhibitor use.

Additionally, we calculated the HRs for outcomes in the reference group (ie, the non–high-risk group) according to baseline variables (Supplemental Table 1). AF type in stroke/SE, falls in major bleeding, and severe liver dysfunction and falls in intracranial hemorrhage showed a significant difference in HRs, even in the reference group; however, the HR value was larger in the high-risk group. In the high-risk group, cerebrovascular disease was the only factor that was not found to be a specific risk factor for stroke/SE.

**DISCUSSION**

Until now, real-world evidence on the effectiveness and safety of OAC agents in very elderly NVAF patients with high bleeding risk has been scarce. In the present subanalysis, we categorized ANAFIE patients as having high bleeding risk by using the inclusion criteria of the ELDERCARE-AF trial, consisting of age of ≥80 years; CHADS2 score of ≥2; and the presence of ≥1 bleeding risk factor: creatinine clearance of 15-30 mL/min; prior bleeding history at critical sites; body weight of ≥45 kg; and continuous single antiplatelet use. The reference group included all other patients. Cumulative incidence rates are shown for the main outcomes of stroke/systemic embolism, major bleeding, cardiovascular events, and all-cause death. The high-risk group had higher cumulative incidences of all these events compared with the reference group (P < 0.001).

ELDERCARE-AF = Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients.
Fibrillation), and ENGAGE-AF TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48). Thus, we deemed it necessary to evaluate the real-world rate of OAC agent use and the outcomes during OAC treatment among elderly Japanese NVAF patients who had high bleeding risk from the ANAFIE registry.

This subanalysis of the ANAFIE registry suggests the usefulness of DOAC agents compared with warfarin and with no OAC agent use in clinical practice in elderly patients at high bleeding risk. First, we found that 22.0% of the ANAFIE patients met the inclusion criteria of the ELDERCARE-AF trial, and this high-risk group of patients had high rates of OAC use (89.0% vs 93.4% in the reference group), with more than a half (58.9%) receiving DOAC agents (vs 69.1% in the reference group). Among the high-risk patients who received DOAC agents, most of the high-risk patients received on-label reduced doses of DOAC agents (71.5%), with a minor proportion receiving off-label low doses (5.9%). It was previously reported that the risk of intracranial hemorrhage during warfarin therapy was higher among Asian patients than White patients, which may explain the tendency of Japanese physicians to prescribe DOAC agents for stroke prevention, even for elderly NVAF patients with high bleeding risk. Of note, the prescribed DOAC doses were appropriately reduced in most cases, whereas the mean TTR during warfarin therapy was 71%. Thus, the prescription of DOAC agents at the doses indicated in the package insert was confirmed for many of the ANAFIE patients who were considered appropriate candidates for OAC therapy, despite the high bleeding risk.

Second, we found that all the events occurred at higher rates in the high-risk group compared with the reference group. This was not surprising because the high-risk group included patients who were older, had more comorbidities, and were at higher risk for stroke and major bleeding.

Third, in the high-risk group, we clearly showed by the multivariate analysis that compared with the nonuse of OAC agents, DOAC agent use was associated with reduced incidences of stroke/SE and all-cause death without significantly increasing major bleeding. Furthermore, the effectiveness and safety of DOAC agents were superior to those of warfarin in reducing stroke/SE, major bleeding, and intracranial hemorrhage. The HR (0.88) of all-cause death was lower with DOAC agents compared with warfarin use, but the difference was not significant. These results were consistent with those seen in the overall ANAFIE registry population. It should be pointed out that the rate for all bleeding events (major bleeding, clinically relevant bleeding, and minor bleeding) was
### TABLE 3 Comparison of Main Outcomes According to Anticoagulant Agent Use in the High-Risk Group

| Event                        | By Type of Anticoagulant Agent n | Events (%) | Univariate Analysis | Multivariate Analysis<sup>a</sup> |
|------------------------------|----------------------------------|------------|---------------------|-----------------------------------|
|                              |                                 |            | HR (95% CI)         | P Value                           |
|                              |                                 |            |                     |                                   |
| Stroke/systemic embolism     | Warfarin vs DOAC agent 4,184     | 135 (3.2)  | 0.71 (0.54-0.92)    | 0.010                             |
|                              | Nonuse of OAC agent vs DOAC agent| 780        | 39 (5.0)            | Reference                         |
|                              |                                 |            |                     |                                   |
| Major bleeding               | Warfarin vs DOAC agent 4,184     | 106 (2.5)  | 0.70 (0.52-0.94)    | 0.018                             |
|                              | Nonuse of OAC agent vs DOAC agent| 780        | 16 (2.1)            | Reference                         |
| All bleeding events<sup>b</sup> | Warfarin vs DOAC agent 4,184     | 405 (9.7)  | 0.91 (0.77-1.07)    | 0.233                             |
|                              | Nonuse of OAC agent vs DOAC agent| 780        | 22 (5.8)            | Reference                         |
| Intracranial hemorrhage      | Warfarin vs DOAC agent 4,184     | 58 (1.4)   | 0.57 (0.39-0.83)    | 0.004                             |
|                              | Nonuse of OAC agent vs DOAC agent| 780        | 13 (1.7)            | Reference                         |
| Gastrointestinal bleeding    | Warfarin vs DOAC agent 4,184     | 58 (1.4)   | 0.81 (0.44-1.47)    | 0.483                             |
|                              | Nonuse of OAC agent vs DOAC agent| 780        | 25 (3.2)            | Reference                         |
| All-cause death              | Warfarin vs DOAC agent 4,184     | 192 (4.6)  | 1.05 (0.82-1.35)    | 0.680                             |
|                              | Nonuse of OAC agent vs DOAC agent| 780        | 25 (3.2)            | Reference                         |
| Cardiovascular death         | Warfarin vs DOAC agent 4,184     | 473 (11.3) | 0.79 (0.69-0.92)    | 0.002                             |
|                              | Nonuse of OAC agent vs DOAC agent| 780        | 113 (14.5)          | Reference                         |
| Net clinical outcome         | Warfarin vs DOAC agent 4,184     | 394 (18.4) | 0.74 (0.62-0.88)    | 0.001                             |

<sup>a</sup>Sex; age; body mass index; history of bleeding; type of AF; systolic blood pressure; severe liver dysfunction; diabetes mellitus; hyperuricemia; heart failure and/or reduced left ventricular ejection fraction; myocardial infarction; cerebrovascular disease; other thromboembolic disease; active cancer; dementia; fall within 1 year; history of catheter ablation; dyslipidemia; creatinine clearance; gastrointestinal diseases; polypharmacy (5 or more); and use of antiarrhythmic agents, proton pump inhibitors, P-glycoprotein inhibitors, and antiplatelet agents were included as an adjustment factor in the model.<sup>b</sup>All bleeding events (major bleeding, clinically relevant bleeding, and minor bleeding).

Abbreviations as in Table 1.
| Outcomes and Factors | Variables | n    | Events (%) | Univariate Analysis | Multivariate Analysis<sup>a</sup> |
|---------------------|-----------|------|------------|---------------------|-------------------------------|
|                     |           |      |            | HR (95% CI)         | P Value                       |
| Stroke/systemic embolism |     |      |            |                     |                               |
| Total               |           | 7,104| 270 (3.8)  | -                   | -                             |
| Sex                 | Male<sup>b</sup> | 3,109| 103 (3.3)  | 1.24 (0.97-1.58)    | 0.089                         |
|                     | Female    | 3,995| 167 (4.2)  | -                   | -                             |
| Body weight         | ≤45 kg    | 2,687| 111 (4.1)  | 1.18 (0.92-1.51)    | 0.197                         |
|                     | >45 kg<sup>b</sup> | 4,088| 145 (3.6)  | -                   | -                             |
| History of major bleeding | Yes   | 681  | 32 (4.7)   | 1.27 (0.87-1.83)    | 0.212                         |
|                     | No<sup>b</sup> | 6,423| 238 (3.7)  | -                   | -                             |
| Type of AF          | Paroxysmal<sup>b</sup> | 2,844| 79 (2.8)   | -                   | -                             |
|                     | Persistent| 1,162| 44 (3.8)   | 1.41 (0.97-2.03)    | 0.070                         |
| Systolic blood pressure | ≤130 mm Hg | 3,725| 133 (3.6)  | -                   | -                             |
|                     | >130 mm Hg to <140 mm Hg | 1,437| 43 (3.0)   | 0.83 (0.59-1.18)    | 0.299                         |
|                     | ≥140 mm Hg | 1,401| 76 (5.4)   | 1.51 (1.14-2.00)    | 0.004                         |
| Severe liver dysfunction | Yes    | 59   | 3 (5.1)    | 1.43 (0.46-4.47)    | 0.534                         |
|                     | No<sup>b</sup> | 7,045| 267 (3.8)  | -                   | -                             |
| Diabetes mellitus   | Yes (HbA<sub>1c</sub> < 6.0%) | 291  | 9 (3.1)    | 0.89 (0.45-1.73)    | 0.728                         |
|                     | Yes (HbA<sub>1c</sub> ≥ 6.0%) | 1,375| 67 (4.9)   | 1.37 (1.04-1.82)    | 0.027                         |
|                     | No<sup>b</sup> | 5,067| 133 (3.2)  | -                   | -                             |
| Hyperuricemia       | Yes       | 1,954| 62 (3.2)   | 0.80 (0.60-1.06)    | 0.122                         |
|                     | No<sup>b</sup> | 5,150| 208 (4.0)  | -                   | -                             |
| Heart failure, reduced LVEF | Yes    | 3,728| 139 (3.7)  | 0.99 (0.78-1.26)    | 0.929                         |
|                     | No<sup>b</sup> | 3,376| 131 (3.9)  | -                   | -                             |
| Myocardial infarction | Yes    | 683  | 22 (3.2)   | 0.84 (0.54-1.29)    | 0.418                         |
|                     | No<sup>b</sup> | 6,421| 248 (3.9)  | -                   | -                             |
| Cerebrovascular disease | Yes    | 2,130| 114 (5.4)  | 1.74 (1.36-2.21)    | 0.001                         |
|                     | No<sup>b</sup> | 4,974| 156 (3.1)  | -                   | -                             |
| Other thromboembolic disease | Yes    | 818  | 39 (4.8)   | 1.31 (0.93-1.84)    | 0.120                         |
|                     | No<sup>b</sup> | 6,286| 231 (3.7)  | -                   | -                             |
| Active cancer       | Yes       | 737  | 22 (3.0)   | 0.79 (0.51-1.22)    | 0.287                         |
|                     | No<sup>b</sup> | 6,367| 248 (3.9)  | -                   | -                             |
| Dementia            | Yes       | 948  | 38 (4.0)   | 1.14 (0.81-1.60)    | 0.465                         |
|                     | No<sup>b</sup> | 6,156| 232 (3.8)  | -                   | -                             |
| Fall within 1 year  | Yes       | 760  | 39 (5.1)   | 1.50 (1.06-2.11)    | 0.020                         |
|                     | No<sup>b</sup> | 5,511| 200 (3.6)  | -                   | -                             |
| Catheter ablation   | Yes       | 324  | 10 (3.1)   | 0.77 (0.41-1.46)    | 0.426                         |
|                     | No<sup>b</sup> | 6,780| 260 (3.8)  | -                   | -                             |
| Antiarrhythmic agents | Yes    | 4,070| 149 (3.7)  | 0.90 (0.71-1.15)    | 0.414                         |
|                     | No<sup>b</sup> | 3,034| 121 (4.0)  | -                   | -                             |
| Proton pump inhibitors | Yes    | 3,272| 116 (3.6)  | 0.88 (0.69-1.12)    | 0.302                         |
|                     | No<sup>b</sup> | 3,832| 154 (4.0)  | -                   | -                             |
| P-glycoprotein inhibitors | Yes    | 140  | 2 (1.4)    | 0.38 (0.10-1.54)    | 0.177                         |
|                     | No<sup>b</sup> | 6,964| 268 (3.9)  | -                   | -                             |
| Dyslipidemia        | Yes       | 3,189| 120 (3.8)  | 0.96 (0.75-1.22)    | 0.715                         |
|                     | No<sup>b</sup> | 3,915| 150 (3.8)  | -                   | -                             |
| Gastrointestinal disease | Yes    | 2,406| 89 (3.7)   | 0.95 (0.74-1.22)    | 0.689                         |
|                     | No<sup>b</sup> | 4,698| 181 (3.9)  | -                   | -                             |
| Antiplatelet agents | Yes (only 1 agent) | 3,024| 112 (3.7)  | 0.92 (0.72-1.17)    | 0.513                         |
|                     | No<sup>b</sup> | 4,060| 158 (3.9)  | -                   | -                             |
| Polypharmacy        | <5 agents<sup>b</sup> | 922  | 30 (3.3)   | -                   | -                             |
|                     | ≥5 agents | 6,053| 233 (3.9)  | 1.19 (0.81-1.74)    | 0.374                         |
| Creatinine clearance | ≥15 mL/min to <30 mL/min | 2,856| 119 (4.2)  | 1.29 (1.00-1.67)    | 0.050                         |
|                     | <30 mL/min | 3,398| 116 (3.4)  | -                   | -                             |

Continued on the next page
| Outcomes and Factors                        | Variables | n     | Events (%) | Univariate Analysis | Multivariate Analysis a |
|-------------------------------------------|-----------|-------|------------|---------------------|-------------------------|
|                                           |           |       |            | HR (95% CI)         | P Value                 |
|                                           |           |       |            |                     |                         |
| Major bleeding                             |           |       |            |                     |                         |
| Total                                      |           | 7,104 | 198 (2.8)  | –                   | –                       |
| Sex                                        | Male b    | 3,109 | 90 (2.9)   | –                   | –                       |
|                                            | Female    | 3,995 | 108 (2.7)  | 0.91 (0.69-1.20)    | 0.513                   |
|                                            |           |       |            | 0.98 (0.69-1.39)    | 0.901                   |
| Body weight                                | ≤45 kg    | 2,687  | 73 (2.7)   | 0.94 (0.70-1.26)    | 0.678                   |
|                                            |           |       |            | 0.98 (0.67-1.45)    | 0.933                   |
|                                            | >45 kg b  | 4,088  | 119 (2.9)  | –                   | –                       |
| History of major bleeding                  | Yes       | 681    | 33 (4.9)   | 1.89 (1.30-2.74)    | <0.001                  |
|                                            | No c      | 4,423  | 165 (2.6)  | –                   | –                       |
| Type of AF                                 | Paroxysmal b | 1,622 | 73 (2.9)   | –                   | –                       |
|                                            | Persistent| 1,162  | 33 (2.8)   | 1.14 (0.75-1.72)    | 0.539                   |
|                                            | Long-standing persistent| 3,098 | 73 (2.4)   | 1.18 (0.87-1.61)    | 0.281                   |
|                                            |           |       |            | 1.02 (0.73-1.42)    | 0.911                   |
| Systolic blood pressure                    | <130 mm Hg| 3,275  | 70 (2.7)   | –                   | –                       |
|                                            | ≥130 mm Hg to <140 mm Hg| 1,437 | 32 (2.2)   | 0.75 (0.50-1.11)    | 0.148                   |
|                                            | ≥140 mm Hg| 1,401  | 40 (2.9)   | 0.95 (0.66-1.36)    | 0.780                   |
|                                            |           |       |            | 1.02 (0.70-1.47)    | 0.935                   |
| Severe liver dysfunction                   | Yes       | 59     | 5 (8.5)    | 3.46 (1.42-8.40)    | 0.006                   |
|                                            | No d      | 7,045  | 193 (2.7)  | –                   | –                       |
| Diabetes mellitus                          | Yes (HbA1c <6.0%)| 291     | 7 (2.4)    | 0.93 (0.43-1.99)    | 0.851                   |
|                                            | Yes (HbA1c ≥6.0%)| 1,375   | 40 (2.9)   | 1.10 (0.77-1.57)    | 0.596                   |
|                                            |           |       |            | 1.14 (0.79-1.66)    | 0.480                   |
| Hyperuricemia                              | Yes       | 1,954  | 57 (2.9)   | 1.09 (0.80-1.48)    | 0.591                   |
|                                            | No e      | 5,076  | 134 (2.6)  | –                   | –                       |
| Heart failure, reduced LVEF               | Yes       | 3,728  | 120 (3.2)  | 1.45 (1.09-1.93)    | 0.011                   |
|                                            | No f      | 3,376  | 78 (2.3)   | –                   | –                       |
| Myocardial infarction                      | Yes       | 683    | 19 (2.8)   | 1.01 (0.63-1.61)    | 0.980                   |
|                                            | No g      | 6,421  | 179 (2.8)  | –                   | –                       |
| Cerebrovascular disease                    | Yes       | 2,130  | 70 (3.3)   | 1.29 (0.96-1.73)    | 0.086                   |
|                                            | No h      | 4,974  | 128 (2.6)  | –                   | –                       |
| Other thromboembolic disease               | Yes       | 818    | 30 (3.7)   | 1.40 (0.95-2.06)    | 0.092                   |
|                                            | No i      | 6,286  | 168 (2.7)  | –                   | –                       |
| Active cancer                              | Yes       | 737    | 28 (3.8)   | 1.48 (1.00-2.21)    | 0.053                   |
|                                            | No j      | 6,367  | 170 (2.7)  | –                   | –                       |
| Dementia                                   | Yes       | 948    | 27 (2.9)   | 1.10 (0.73-1.65)    | 0.643                   |
|                                            | No k      | 6,156  | 171 (2.8)  | –                   | –                       |
| Fall within 1 year                         | Yes       | 760    | 43 (5.7)   | 2.67 (1.89-3.78)    | <0.001                  |
|                                            | No l      | 5,511  | 125 (2.3)  | –                   | –                       |
| Catheter ablation                          | Yes       | 324    | 11 (3.4)   | 1.19 (0.65-2.18)    | 0.578                   |
|                                            | No m      | 6,780  | 187 (2.8)  | –                   | –                       |
| Antiarrhythmic agents                      | Yes       | 4,070  | 104 (2.6)  | 0.81 (0.61-1.07)    | 0.144                   |
|                                            | No n      | 3,034  | 94 (3.1)   | –                   | –                       |
| Proton pump inhibitors                      | Yes       | 3,272  | 91 (2.8)   | 1.00 (0.75-1.32)    | 0.983                   |
|                                            | No o      | 3,832  | 107 (2.8)  | –                   | –                       |
| P-glycoprotein inhibitors                   | Yes       | 140    | 4 (1.4)    | 0.53 (0.13-2.13)    | 0.372                   |
|                                            | No p      | 6,964  | 196 (2.8)  | –                   | –                       |
| Dyslipidemia                                | Yes       | 3,189  | 85 (2.7)   | 0.90 (0.68-1.19)    | 0.458                   |
|                                            | No q      | 3,915  | 113 (2.9)  | –                   | –                       |
| Gastrointestinal disease                   | Yes       | 2,406  | 77 (3.2)   | 1.24 (0.93-1.64)    | 0.147                   |
|                                            | No r      | 4,698  | 121 (2.6)  | –                   | –                       |
| Antiplatelet agents (only 1 agent)         | Yes       | 3,024  | 73 (2.4)   | 0.76 (0.57-1.02)    | 0.068                   |
|                                            | No s      | 4,060  | 124 (3.1)  | –                   | –                       |
| Polypharmacy                               | <5 agents b | 922    | 21 (2.3)   | –                   | –                       |
|                                            | ≥5 agents | 6,053  | 171 (2.8)  | 1.25 (0.79-1.97)    | 0.336                   |
| Creatinine clearance                       | ≥15 mL/min to <30 mL/min| 2,856 | 82 (2.9)   | 1.11 (0.82-1.49)    | 0.492                   |
|                                            | ≥30 mL/min b | 3,398 | 93 (2.7)   | –                   | –                       |

Intracranial hemorrhage                     |           |       |            |                     |                         |
| Total                                      |           | 7,104  | 122 (1.7)  | –                   | –                       |
| Sex                                        | Male b    | 3,109  | 55 (1.8)   | –                   | –                       |
|                                            | Female    | 3,995  | 67 (1.7)   | 0.92 (0.65-1.32)    | 0.660                   |

Continued on the next page
### TABLE 4 Continued

| Outcomes and Factors | Variables | n Events (%) | Univariate Analysis | Multivariate Analysis<br>(HR (95% CI) P Value) | Multivariate Analysis<br>(HR (95% CI) P Value) |
|----------------------|-----------|--------------|---------------------|-----------------------------------------------|-----------------------------------------------|
|                      |           |              | HR (95% CI) P Value | HR (95% CI) P Value | |
| Body weight          | ≤45 kg    | 2,687 55 (1.8) | 1.30 (0.90-1.86) 0.158 | 1.50 (0.91-2.47) 0.114 | |
|                      | >45 kga   | 4,088 64 (1.6) | – | – | |
| History of major bleeding | Yes | 681 18 (2.6) | 1.62 (0.98-2.67) 0.059 | 1.40 (0.79-2.47) 0.252 | |
|                      | Nob | 4,623 104 (1.6) | – | – | |
| Type of AF           | Paroxysmalb | 2,844 45 (1.6) | – | – | |
|                      | Persistent | 1,162 19 (1.6) | 1.06 (0.62-1.82) 0.819 | 1.04 (0.59-1.83) 0.886 | |
|                      | Long-standing persistent | 3,098 58 (1.9) | 1.21 (0.82-1.79) 0.333 | 1.12 (0.73-1.72) 0.594 | |
| Systolic blood pressure | <130 mm Hg | 3,725 69 (1.9) | – | – | |
|                      | ≥130 mm Hg to <140 mm Hg | 1,437 15 (1.0) | 0.56 (0.32-0.98) 0.041 | 0.61 (0.35-1.07) 0.087 | |
|                      | ≥140 mm Hg | 1,401 29 (2.1) | 1.10 (0.71-1.70) 0.668 | 1.16 (0.74-1.83) 0.508 | |
| Severe liver dysfunction | Yes | 59 4 (6.8) | 4.42 (1.63-11.97) 0.004 | 3.55 (1.27-9.89) 0.015 | |
|                      | Nob | 5,067 84 (1.7) | – | – | |
| Diabetes mellitus | Yes (HbA1c < 6.0%) | 291 5 (1.7) | 1.06 (0.43-2.61) 0.900 | 0.95 (0.38-2.37) 0.910 | |
|                      | Yes (HbA1c ≥ 6.0%) | 1,375 22 (1.6) | 0.96 (0.60-1.54) 0.867 | 1.04 (0.64-1.71) 0.863 | |
|                      | Nob | 5,067 84 (1.7) | – | – | |
| Hyperuricemia | Yes | 1,954 35 (1.8) | 1.09 (0.73-1.61) 0.683 | 1.04 (0.68-1.61) 0.848 | |
|                      | Nob | 5,150 87 (1.7) | – | – | |
| Heart failure, reduced LVEF | Yes | 3,728 69 (1.9) | 1.22 (0.85-1.75) 0.271 | 1.07 (0.72-1.59) 0.730 | |
|                      | Nob | 3,376 53 (1.6) | – | – | |
| Myocardial infarction | Yes | 683 11 (1.6) | 0.94 (0.50-1.74) 0.840 | 0.89 (0.44-1.81) 0.746 | |
|                      | Nob | 6,421 111 (1.7) | – | – | |
| Cerebrovascular disease | Yes | 2,130 47 (2.2) | 1.48 (1.03-2.13) 0.036 | 1.43 (0.97-2.11) 0.075 | |
|                      | Nob | 4,974 75 (1.7) | – | – | |
| Other thromboembolic disease | Yes | 818 16 (2.0) | 1.17 (0.69-1.98) 0.552 | 1.13 (0.65-1.96) 0.667 | |
|                      | Nob | 6,286 106 (1.7) | – | – | |
| Active cancer | Yes | 737 15 (2.0) | 1.26 (0.73-2.16) 0.405 | 1.03 (0.58-1.83) 0.917 | |
|                      | Nob | 6,367 107 (1.7) | – | – | |
| Dementia | Yes | 948 18 (1.9) | 1.21 (0.73-1.99) 0.461 | 1.07 (0.64-1.81) 0.788 | |
|                      | Nob | 6,156 104 (1.7) | – | – | |
| Fall within 1 year | Yes | 760 29 (3.8) | 3.08 (2.00-4.74) <0.001 | 2.61 (1.66-4.11) <0.001 | |
|                      | Nob | 5,511 73 (1.3) | – | – | |
| Catheter ablation | Yes | 324 8 (2.5) | 1.41 (0.69-2.90) 0.343 | 1.63 (0.78-3.43) 0.196 | |
|                      | Nob | 6,780 114 (1.7) | – | – | |
| Antithrombotic agents | Yes | 4,070 66 (1.6) | 0.87 (0.61-1.24) 0.429 | 0.92 (0.63-1.34) 0.657 | |
|                      | Nob | 3,034 56 (1.9) | – | – | |
| Proton pump inhibitors | Yes | 3,272 44 (1.3) | 0.66 (0.46-0.95) 0.027 | 0.66 (0.45-0.99) 0.045 | |
|                      | Nob | 3,832 78 (2.0) | – | – | |
| P-glycoprotein inhibitors | Yes | 140 2 (1.4) | 0.87 (0.22-3.52) 0.845 | 0.92 (0.23-3.78) 0.911 | |
|                      | Nob | 6,964 120 (1.7) | – | – | |
| Dyslipidemia | Yes | 3,189 56 (1.8) | 1.01 (0.71-1.45) 0.943 | 1.12 (0.76-1.67) 0.558 | |
|                      | Nob | 3,916 78 (1.7) | – | – | |
| Gastrointestinal disease | Yes | 2,406 45 (1.9) | 1.13 (0.78-1.63) 0.511 | 1.04 (0.69-1.55) 0.857 | |
|                      | Nob | 4,698 77 (1.6) | – | – | |
| Antithrombotic agents | Yes (only 1 agent) | 3,024 44 (1.4) | 0.74 (0.51-1.07) 0.112 | 0.83 (0.50-1.38) 0.471 | |
|                      | Nob | 4,060 77 (1.9) | – | – | |
| Polypharmacy | <5 agents | 922 18 (2.0) | – | – | |
|                      | ≥5 agents | 6,053 98 (1.6) | 0.83 (0.50-1.37) 0.470 | 0.88 (0.51-1.53) 0.654 | |
| Creatinine clearance | ≤15 mL/min to <30 mL/min | 2,856 47 (1.7) | 1.02 (0.70-1.50) 0.912 | 0.87 (0.56-1.37) 0.558 | |
|                      | ≤30 mL/min | 3,398 58 (1.7) | – | – | |

*Sex; body weight; history of bleeding; type of AF; systolic blood pressure; severe liver dysfunction; diabetes mellitus; hyperuricemia; heart failure and/or reduced LVEF; myocardial infarction; cerebrovascular disease; other thromboembolic disease; active cancer; dementia; fall within 1 year; history of catheter ablation; dyslipidemia; creatinine clearance; gastrointestinal diseases; polypharmacy (5 or more); anticoagulant agent; and use of antithrombotic agents, proton pump inhibitors, P-glycoprotein inhibitors, and antiplatelet agents were included as an adjustment factor in the model. Type of anticoagulant agents were included in the multivariate analysis model as an explanatory factor. Reference. HbA1c = glycosylated hemoglobin; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.
significantly higher in the DOAC agent use than in the nonuse-of-OAC-agents group. A careful observation should be required even when DOAC agents are selected in high-risk group patients.

For the higher incidence of major bleeding in the high-risk group than in the reference group, as expected, multivariate analysis for the baseline characteristics of high-risk patients revealed that a history of major bleeding, severe liver dysfunction, and falls within 1 year were significant independent predictors for major bleeding. Based on these findings, we suggest that careful observation for the occurrence of major bleeding should be required for the management of elderly high-risk patients with these clinical characteristics when OAC agent use is considered.

The ELDERCARE-AF trial evaluated the efficacy and safety of very-low-dose edoxaban (15 mg) vs placebo and demonstrated that edoxaban was superior to placebo for preventing stroke/SE without a significant increase in major bleeding events. It should be noted that all ELDERCARE-AF patients were considered inappropriate for standard OAC therapy at approved doses. In fact, 57% of the patients had not received any OAC therapy before participating in the trial. In contrast, the remaining patients had been previously treated with OAC agents but discontinued DOAC agents or were treated with warfarin at an insufficient control level. The present subanalysis of the ANAFIE registry defined patients with similar characteristics to patients included in the ELDERCARE-AF trial as the high-risk group. However, considering that 58.9% of these patients received DOAC agents and most of them were prescribed on-label reduced DOAC agent doses at study entry, the risk of bleeding might have been lower among those patients in the present analysis than among patients in the ELDERCARE-AF trial. Further studies are needed to evaluate the use of OAC therapy, including very-low-dose edoxaban in the patient group in which no OAC agent was used, presumably because of the extremely high bleeding risk.

**STUDY LIMITATIONS.** The main limitation of the present analysis is that it is a post hoc evaluation. Additionally, in this subanalysis, patients with a high risk of bleeding were grouped according to the definition used in the ELDERCARE-AF trial, but the mean HAS-BLED score in the high-risk group of the ANAFIE registry was 2.2. Thus, the high bleeding risk in the high-risk group was not linked to the HAS-BLED score. Furthermore, patients with a CrCl of <15 mL/min or undergoing dialysis were not included in the high-risk group for bleeding in this study to verify the significance of DOAC agents because they are not indicated for DOAC agents. Therefore, this may have affected the power of the analysis. Because the ANAFIE registry enrolled patients eligible for OAC therapy, comparisons with the data from the ELDERCARE-AF trial, which enrolled patients who were not eligible for standard OAC therapy at approved doses, are limited. Although many high-risk group patients prescribed with DOAC agents (76%) received appropriate on-label doses, other patients (13%) received inappropriately reduced off-label doses while showing similar 2-year incidences of stroke/SE, major bleeding, and all-cause mortality. Additional limitations of the ANAFIE registry have been reported previously and include the enrollment of only Japanese NVAF patients; the fact that variables such as changes in OAC agent during follow-up were not considered; the fact that TTR for warfarin was reported at baseline but was not re-evaluated during the follow-up; and the fact that the study did not limit the inclusion of patients who had already been receiving anticoagulant treatment before enrollment. Finally, outcomes for warfarin-treated patients were not reported according to individual TTR groups (ie, <40%, 40% to <60%, 60% to <80%, and ≥80%) or international normalized ratio, and we are unable to speculate as to how this may have affected the results observed.

**CONCLUSIONS**

Patients from the ANAFIE registry at high bleeding risk had higher incidences of stroke/SE, major bleeding, intracranial hemorrhage, gastrointestinal bleeding, cardiovascular events, and all-cause death than patients in the reference group, despite a high prevalence of OAC therapy (89.0%). Our data indicate that DOAC agent use was associated with reduced risks without significantly increasing major bleeding events compared with nonuse of OAC agents in elderly NVAF patients at high bleeding risk. The present results also indicate that DOAC agent use was superior to warfarin in reducing stroke/SE, major bleeding, and intracranial hemorrhage in these patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our findings indicate that, compared with nonuse of oral anticoagulant agents, DOAC agent use may be associated with reduced risks without significantly increasing major bleeding events among elderly non-valvular atrial fibrillation patients at high bleeding risk.

TRANSLATIONAL OUTLOOK: Further studies are warranted to confirm that DOAC agent use is superior to warfarin for reducing stroke/systemic embolism, major bleeding, and intracranial hemorrhage in elderly patients with nonvalvular atrial fibrillation and high bleeding risk.

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

**APPENDIX** For a supplemental table, please see the online version of this paper.