


# BMJ Open Background characteristics and anticoagulant usage patterns of elderly non-valvular atrial fibrillation patients in the ANAFIE registry: a prospective, multicentre, observational cohort study in Japan

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## ABSTRACT

**Objective** To explore anticoagulant usage patterns stratified by stroke and bleeding risk in elderly patients with non-valvular atrial fibrillation (NVAF).

**Design** Prospective, multicentre, observational cohort study.

**Setting** The real-world All Nippon AF In the Elderly (ANAFIE) registry.

**Participants** Japanese patients aged  $\geq 75$  years with NVAF (n=32 726).

**Outcome measures** The distribution of stroke and bleeding risk scores, and the selection of anticoagulant regimen for patients at high stroke and bleeding risk.

**Results** Overall, 18 185 (55.6%) patients had a high risk of stroke (CHADS<sub>2</sub> score  $\geq 3$ ). Of these, 12 561 (38.4% of the total ANAFIE population) had a low bleeding risk (HAS-BLED  $\leq 2$ ) and 5624 (17.2%) had a high bleeding risk (HAS-BLED  $\geq 3$ ). Significant differences were noted between the high versus low bleeding risk groups in sex, height, weight, systolic blood pressure and rates of abnormality of lipid metabolism, gastrointestinal disease, cerebrovascular disorders, chronic kidney disease, angina pectoris, respiratory disease, primary malignant tumour, dementia and fall history within the past year (all  $p < 0.0001$ ).

Patients with high stroke and bleeding risks had a lower anticoagulant usage rate versus the low bleeding risk group, and 8.7% and 5.8%, respectively, were not receiving any anticoagulant ( $p < 0.0001$ ). Patients in the high bleeding risk group had a higher usage of warfarin versus the low bleeding risk group ( $p < 0.0001$ ); more patients (14.0%) in the high bleeding risk group receiving warfarin had time in the therapeutic range  $< 40\%$ , versus those in the low bleeding risk group (11.6%,  $p = 0.0146$ ). Direct-acting oral anticoagulants (DOACs) were used less in the high bleeding risk group, without notable differences in the DOAC dose distribution between the two groups.

**Conclusions** In elderly NVAF patients at high stroke risk, significant demographic and clinical differences were

## Strengths and limitations of this study

- This large-scale analysis of the All Nippon AF In the Elderly registry provides real-world data on anticoagulant therapy use by stroke and bleeding risk score distribution in elderly patients with non-valvular atrial fibrillation, who tend to be excluded from clinical trials.
- Direct oral anticoagulant dose distribution data will promote critical discussion on current and future treatment paradigms.
- Extrapolation of the study results may be limited by the observational, registry-based design and the enrolment of only Japanese patients.
- The use of the overlapping CHADS<sub>2</sub> and HAS-BLED measures to classify patients into risk groups may have introduced an element of selection bias into the analysis.
- Anticoagulant dose reductions according to approved dose reduction criteria for individual drugs or other reasons were not considered in this analysis, and the impact of unwarranted dose reductions on event rates remains to be determined.

observed according to bleeding risk. Administration of low-dose DOACs was frequent, but the dose distribution was unaffected by bleeding risk.

**Trial registration number** UMIN000024006 (<http://www.umin.ac.jp/>).

## INTRODUCTION

During the past half-century, Japan has experienced rapid ageing of its population; the percentage of Japanese individuals aged  $\geq 65$  years was 7% in 1970 and has since risen to

27.7%.<sup>1</sup> Any population in which >20% of individuals are aged  $\geq 65$  years is classified as a 'super-aged society', and in Japan, the proportion of elderly individuals (aged  $\geq 65$  years) is expected to reach 38% by 2050.<sup>1</sup>

Alongside longer lifespans, it is expected that the incidence of age-related diseases will increase.<sup>2,3</sup> These include non-valvular atrial fibrillation (NVAf), which is a common arrhythmia in elderly patients and has been described as an independent risk factor for stroke.<sup>4,5</sup> Older NVAf patients are particularly vulnerable to experiencing a stroke since both age and AF are independent risk factors.<sup>6</sup> Among patients with AF, stroke risk is mitigated via the usage of anticoagulants; however, treatment can be associated with increased risk of bleeding.<sup>7</sup> Therefore, clinical management decisions regarding appropriate thromboprophylaxis for NVAf patients require the assessment of stroke risk and bleeding risk in each patient, using validated measures such as CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc (for stroke) and HAS-BLED (for bleeding) scores.<sup>8</sup> However, while anticoagulation has been demonstrated to effectively prevent stroke in patients with NVAf,<sup>9-11</sup> elderly patients are often undertreated, despite this population having a higher risk for stroke.<sup>12,13</sup>

Despite the importance of initiating appropriate anticoagulation therapy to reduce adverse outcomes for patients, to date, there are few reports of studies that have investigated the actual state of anticoagulant therapy according to stroke and bleeding risk score distribution in elderly NVAf patients. As the Japanese population continues to age and AF becomes more common, it is important that physicians have a clear understanding of the differences in patient clinical characteristics and the prescription of anticoagulant therapy depending on the degree of bleeding risk (HAS-BLED score) to ensure optimal management of elderly AF patients, who are at a high risk of stroke (CHADS<sub>2</sub> score  $\geq 3$  points) and who require aggressive anticoagulant therapy. Thus, this study aimed to clarify the distribution of stroke risk (CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc scores), bleeding risk (HAS-BLED scores), and physician's choice of anticoagulant regimen in patients aged  $\geq 75$  years with NVAf in the real-world clinical situation. For this purpose, we used prospective data collected in the large-scale All Nippon AF In the Elderly (ANAFIE) registry.<sup>13,14</sup> Subsequently, we performed an in-depth investigation of those patients at high risk of stroke (who would generally be candidates for aggressive anticoagulant therapy), with the aim of identifying any differences in treatment according to the degree of bleeding risk (high vs low).

## METHODS

### Study design

The ANAFIE registry was a prospective, multicentre, observational cohort study. Enrolment occurred between October 2016 and January 2018. During this period, 32 726 elderly patients aged  $\geq 75$  years with NVAf were registered. Patients were followed up for 24 months, and data

were collected at 12 and 24 months. Full details of the ANAFIE study design have been published.<sup>13</sup>

### Patients

Enrolled patients were men or women aged  $\geq 75$  years who provided informed consent to participate in the study, with a definitive diagnosis of NVAf based on electrocardiograms, and who were able to attend study visits. Patients were excluded if they were participating in an interventional study, if they had a definitive diagnosis of mitral stenosis, had undergone artificial valvular replacement, had a history of stroke, myocardial infarction, cardiac intervention, heart failure, or bleeding requiring hospitalisation within 1 month of enrolment, had a life expectancy of less than 1 year, and if the investigator considered patient participation inappropriate.

### Treatment

No treatment was mandated. Anticoagulation therapy (ie, anticoagulant used and prescribed dose) and other drugs used were determined by the patient's treating physician according to routine clinical practice in Japan. Patients could be receiving vitamin K antagonists (VKA), such as warfarin, or non-vitamin K anticoagulants such as direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban and edoxaban. Of note, DOACs act directly on specific proteins of the coagulation cascade. VKA inhibit the synthesis of vitamin K-dependent coagulation factors. Thus, reaching the therapeutic range is needed to obtain the anticoagulant effect of VKA, which may be affected by drug and food interactions. In contrast, DOACs result in a more predictable and stable anticoagulant effect, while showing comparable efficacy to warfarin.<sup>15</sup>

### Observation items

Overall, in the ANAFIE registry, data were collected on patient background characteristics, type of AF, anticoagulation therapy details, use of concomitant drugs and baseline laboratory data. Composite of stroke and systemic embolism was the primary outcome. Major bleeding, stroke, systemic embolism, haemorrhagic stroke, intracranial haemorrhage, cardiovascular events, death from cardiovascular disease and all-cause death were the secondary outcomes.

For this analysis of ANAFIE data, patients were stratified based on their stroke risk. High stroke risk was defined as CHADS<sub>2</sub> score  $\geq 3$ . Patients at high stroke risk were then subdivided into bleeding risk analysis groups. Low bleeding risk was defined as HAS-BLED  $\leq 2$ , and the high bleeding risk was defined as HAS-BLED  $\geq 3$ ; previous AF studies have selected these cut-offs to identify high-risk and low-risk patients.<sup>16</sup> Confirmatory analyses were conducted using the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score, where a score  $\geq 5$  indicated high stroke risk.

### Patient and public involvement

No patients were involved.

## Statistical analysis

The estimated sample size was 30 000 patients, and details of the sample size calculation were previously described.<sup>13</sup> The analysis set included all enrolled patients who met the inclusion criteria. For this analysis, frequency tables were created for categorical variables, and summary statistics were calculated for continuous variables. Subgroups were defined by the CHADS<sub>2</sub> score, CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and HAS-BLED score. Between-group differences were evaluated for patients at high risk of stroke according to the bleeding risk, and p values were calculated using the  $\chi^2$  test or t-test. No imputations were made for missing data, which were not included in the analyses. A two-sided p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS V.9.4 (SAS Institute).

## RESULTS

### Patient background characteristics

Table 1 shows the key patient background characteristics for the total population and populations stratified by stroke and bleeding risks. Among 32 726 NVAF patients aged  $\geq 75$  years, 18 185 (55.6%) were found to have a high risk of stroke (CHADS<sub>2</sub> score  $\geq 3$ ) and 21.1% had a HAS-BLED score  $\geq 3$ .

Among patients at high risk of stroke, 12 561 patients (38.4% of the total ANAFIE population) were classified as having a low bleeding risk (HAS-BLED  $\leq 2$ ) and 5624 patients (17.2%) were classified as having a high bleeding risk (HAS-BLED  $\geq 3$ ). Patients at high risk of bleeding were more likely to be male, taller, heavier and had higher systolic blood pressure, compared with the low bleeding risk group (p < 0.0001 for all). The high bleeding risk group had significantly higher rates of abnormality of lipid metabolism, gastrointestinal disease, cerebrovascular disorders, chronic kidney disease (CKD), severe liver dysfunction, angina pectoris, myocardial infarction, respiratory disease, primary malignant tumour, dementia and fall history within the past year compared with the low bleeding risk group (p < 0.0001 for all). The prevalence of heart failure was 10% higher in the low bleeding risk group compared with patients in the high bleeding risk group (p < 0.0001), and the prevalence of hypertension and diabetes mellitus was high in the group with low bleeding risk (table 2).

Data from the confirmatory analysis using CHA<sub>2</sub>DS<sub>2</sub>-VASc score are shown in online supplemental tables S1,2. Overall, 14 362 (43.9%) of ANAFIE patients had a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 5$  (indicating high risk of stroke).

### Anticoagulant administration status in patients at high risk of stroke by bleeding risk

Figure 1 shows the anticoagulant use status in each group. The proportion of patients who used anticoagulants was lower among those with both high stroke and high bleeding risks compared with the low bleeding risk group (91.3% vs 94.2%, p < 0.0001). Patients in the

high bleeding risk group had significantly higher usage of warfarin compared with the low bleeding risk group (p < 0.0001).

Overall, the use of direct-acting anticoagulants (DOACs) was lower in the high bleeding risk group (67.5% vs 71.5%, p < 0.0001), but both bleeding risk groups used the same type of agents to similar extents, with around one-quarter using apixaban and <10% using dabigatran. The analysis using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score confirmed these results (online supplemental figure S1).

### Average time in the therapeutic range in patients who received warfarin

The average time in the therapeutic range (TTR) in patients who received warfarin in each group is shown in figure 2. Patients with both high stroke and high bleeding risks had a higher usage rate of warfarin compared with patients in the low bleeding risk group (29.6% vs 26.9%, figure 1), and the TTRs were 73.6 $\pm$ 30.4% versus 75.9 $\pm$ 29.2%, respectively. In the high bleeding risk group, 14.0% of patients had TTR <40%, compared with 11.6% in the low bleeding risk group (p = 0.0146). Data for the analysis according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score are shown in online supplemental figure S2.

### Dosage of DOACs by group

Figure 3 and online supplemental figure S3 show the doses of DOACs received in each bleeding risk group. There were no notable differences in the dose distribution of DOACs between the two groups. The majority of patients were receiving the reduced dose of DOAC, and similar proportions of patients in each bleeding risk group were receiving standard doses for each DOAC.

Online supplemental table S3 shows further details on the doses of DOACs received by patients at high risk of stroke (CHADS<sub>2</sub> score  $\geq 3$ ) and low (HAS-BLED  $\leq 2$ ) or high risk of bleeding (HAS-BLED  $\geq 3$ ). For all DOACs, the proportions of patients receiving a reduced DOAC dose was higher than that for patients receiving the standard or off-label dose in both the high-bleeding and low-bleeding risk groups. The proportions of patients receiving off-label DOAC doses, standard DOAC doses and reduced DOAC doses were similar regardless of the bleeding risk.

## DISCUSSION

Our data indicate that, overall, 55.6% of ANAFIE patients had a CHADS<sub>2</sub> score  $\geq 3$ , indicating a high risk of stroke, and 21.1% had a HAS-BLED score  $\geq 3$ , indicating a high risk of bleeding. When patients with a CHADS<sub>2</sub> score  $\geq 3$  were subdivided into high-bleeding or low-bleeding risk groups (based on the HAS-BLED score), approximately one-sixth of ANAFIE patients (17.2%) were found to meet the criteria for high stroke risk and high bleeding risk, which is a large proportion of NVAF patients.

As the CHADS<sub>2</sub> measure uses factors such as hypertension, older age, and previous stroke symptoms to classify patients according to stroke risk, it was expected that

Table 1 Patient background characteristics

	CHADS <sub>2</sub> score				HAS-BLED score				High stroke risk					
	≤1		2		≥3		≤2		≥3		High		Low	
	n	mean±SD	n	mean±SD	n	mean±SD	n	mean±SD	n	mean±SD	n	mean±SD	n	mean±SD
Patients	3002	11 539	18 185	25 810	6916				5624	12 561				
Age, years	80.4±4.5	81.2±4.7	81.8±4.9	81.4±4.8	81.8±4.9	<0.0001			81.9±4.9	81.8±4.9	<0.0001		81.8±4.9	0.0843
Male	1816 (60.5)	6340 (54.9)	10 577 (58.2)	13 745 (53.3)	4988 (72.1)	0.2344			3987 (70.9)	6590 (52.5)	<0.0001		6590 (52.5)	<0.0001
Height, cm	158.8±9.4	157.2±9.4	157.0±9.5	156.8±9.6	158.9±9.1	<0.0001			158.7±9.2	156.2±9.6	<0.0001		156.2±9.6	<0.0001
Weight, kg	56.5±10.4	57.6±10.9	58.2±11.4	57.4±11.2	59.2±11.0	<0.0001			59.2±11.1	57.7±11.5	<0.0001		57.7±11.5	<0.0001
BMI, kg/m <sup>2</sup>	22.3±3.2	23.2±3.4	23.5±3.7	23.3±3.6	23.4±3.5	<0.0001			23.5±3.5	23.6±3.7	0.1025		23.6±3.7	0.0631
SBP, mm Hg	125.1±16.1	128.6±16.9	127.0±17.2	126.8±6.1	129.6±20.0	0.0712			129.0±19.3	126.0±16.1	<0.0001		126.0±16.1	<0.0001
DBP, mm Hg	71.3±11.1	71.5±11.5	70.0±11.8	70.6±11.4	70.8±12.6	<0.0001			70.5±12.4	69.8±11.5	0.2389		69.8±11.5	0.0008
CCr, mL/min	53.2±16.5	50.2±17.7	46.7±24.3	50.1±22.6	42.7±17.2	<0.0001			42.6±17.2	48.6±26.8	<0.0001		48.6±26.8	<0.0001
Smoking status						<0.0001					<0.0001			<0.0001
Never	1560 (52.0)	6068 (52.6)	8724 (48.0)	13 509 (52.3)	2843 (41.1)				2335 (41.5)	6389 (50.9)			6389 (50.9)	
Quit	916 (30.5)	3313 (28.7)	5791 (31.8)	7061 (27.4)	2959 (42.8)				2347 (41.7)	3444 (27.4)			3444 (27.4)	
Continuing	115 (3.8)	421 (3.6)	714 (3.9)	862 (3.3)	388 (5.6)				309 (5.5)	405 (3.2)			405 (3.2)	
Unknown	411 (13.7)	1737 (15.1)	2956 (16.3)	4378 (17.0)	726 (10.5)				633 (11.3)	2323 (18.5)			2323 (18.5)	
Alcohol intake						0.9421					0.2389			<0.0001
Daily basis	491 (16.4)	2113 (18.3)	3243 (17.8)	3331 (12.9)	2516 (36.4)				1852 (32.9)	1391 (11.1)			1391 (11.1)	
Sometimes	626 (20.9)	2100 (18.2)	3199 (17.6)	4927 (19.1)	998 (14.4)				852 (15.1)	2347 (18.7)			2347 (18.7)	
Never	1433 (47.7)	5422 (47.0)	8599 (47.3)	12 780 (49.5)	2674 (38.7)				2282 (40.6)	6317 (50.3)			6317 (50.3)	
Unknown	452 (15.1)	1904 (16.5)	3144 (17.3)	4772 (18.5)	728 (10.5)				638 (11.3)	2506 (20.0)			2506 (20.0)	

Data are shown as mean±SD or n (%).

\*In the population at high risk of stroke (CHADS<sub>2</sub> ≥2), high bleeding risk is HAS-BLED ≥3; low bleeding risk is HAS-BLED ≤2.

†P value for the trend was calculated using the Jonckheere-Terpstra test for continuous variables, the Cochran-Armitage test for two-level categorical variables, and the correlation statistic of the Cochran-Mantel-Haenszel test for categorical variables with three or more levels. Unknowns were excluded from the analysis.

‡P value was calculated using the two-sample t-test for continuous variables and the  $\chi^2$  test for categorical variables. Unknowns were excluded from the analysis.

BMI, body mass index; CCr, creatinine clearance; DBP, diastolic blood pressure; SBP, systolic blood pressure.

**Table 2** Comorbidities classified by bleeding risk in the population at high risk of stroke (CHADS<sub>2</sub> ≥3)

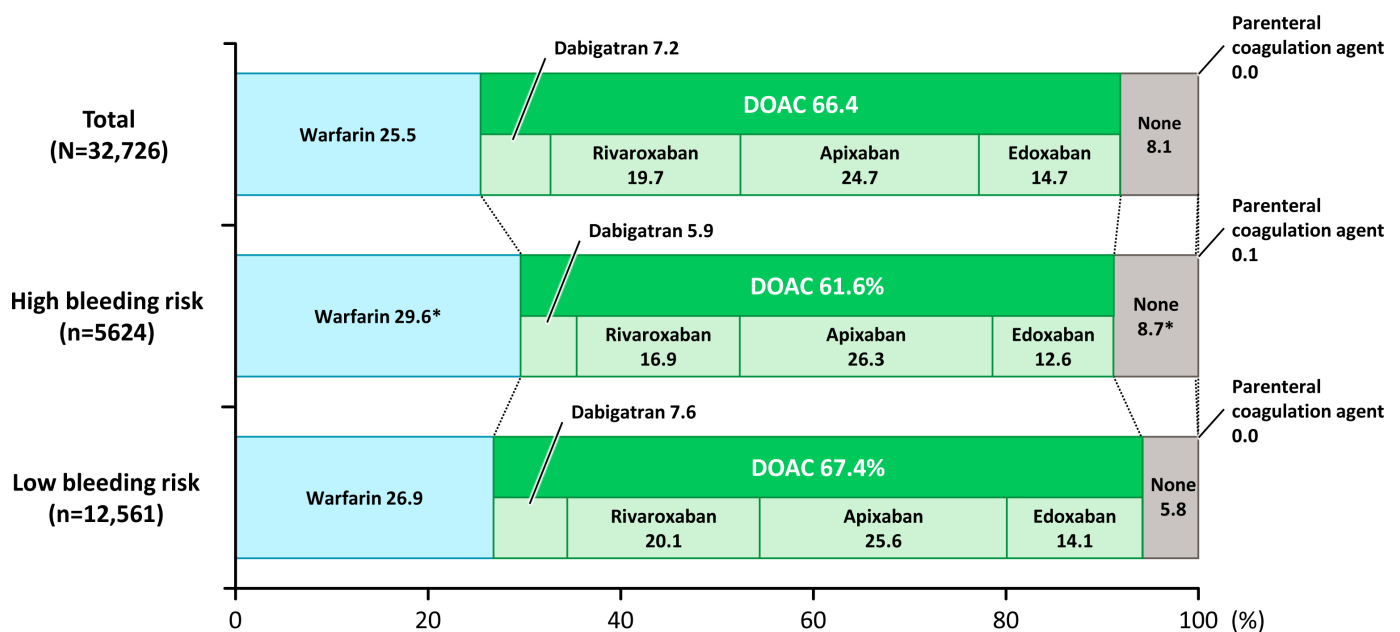
Comorbidity‡	Bleeding risk*		P value†
	High (n=5624)	Low (n=12 561)	
Hypertension	4779 (85.0)	10 863 (86.5)	0.0068
Abnormality of lipid metabolism	2869 (51.0)	5756 (45.8)	<0.0001
Heart failure	2936 (52.2)	7971 (63.5)	<0.0001
Gastrointestinal disease	2249 (40.0)	3732 (29.7)	<0.0001
Diabetes mellitus	2372 (42.2)	5887 (46.9)	<0.0001
Cerebrovascular disorders	3910 (69.5)	3106 (24.7)	<0.0001
Hyperuricaemia	2084 (37.1)	2954 (23.5)	<0.0001
Chronic kidney disease	2862 (50.9)	1701 (13.5)	<0.0001
Severe liver dysfunction	111 (2.0)	78 (0.6)	<0.0001
Angina pectoris	1431 (25.4)	2370 (18.9)	<0.0001
Myocardial infarction	650 (11.6)	701 (5.6)	<0.0001
Respiratory disease	888 (15.8)	1752 (13.9)	0.0011
Primary malignant tumour	850 (15.1)	1274 (10.1)	<0.0001
Thrombosis and embolism-related diseases	891 (15.8)	1254 (10.0)	<0.0001
Dementia	676 (12.0)	1068 (8.5)	<0.0001
Fall history within the past year	594 (10.6)	962 (7.7)	<0.0001

Data are shown as n (%).

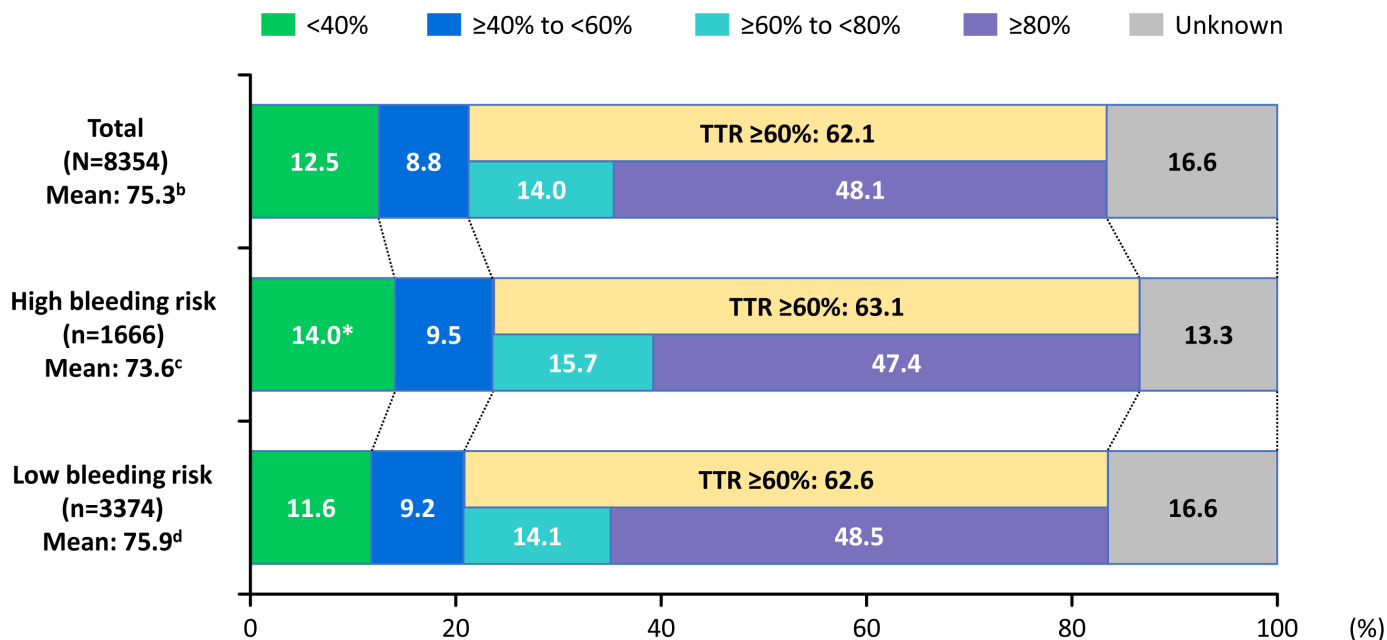
\*High bleeding risk is HAS-BLED ≥3; low bleeding risk is HAS-BLED ≤2.

†P values were calculated using the two-sample t-test for continuous variables and the  $\chi^2$  test for categorical variables. Unknowns were excluded from the analysis.

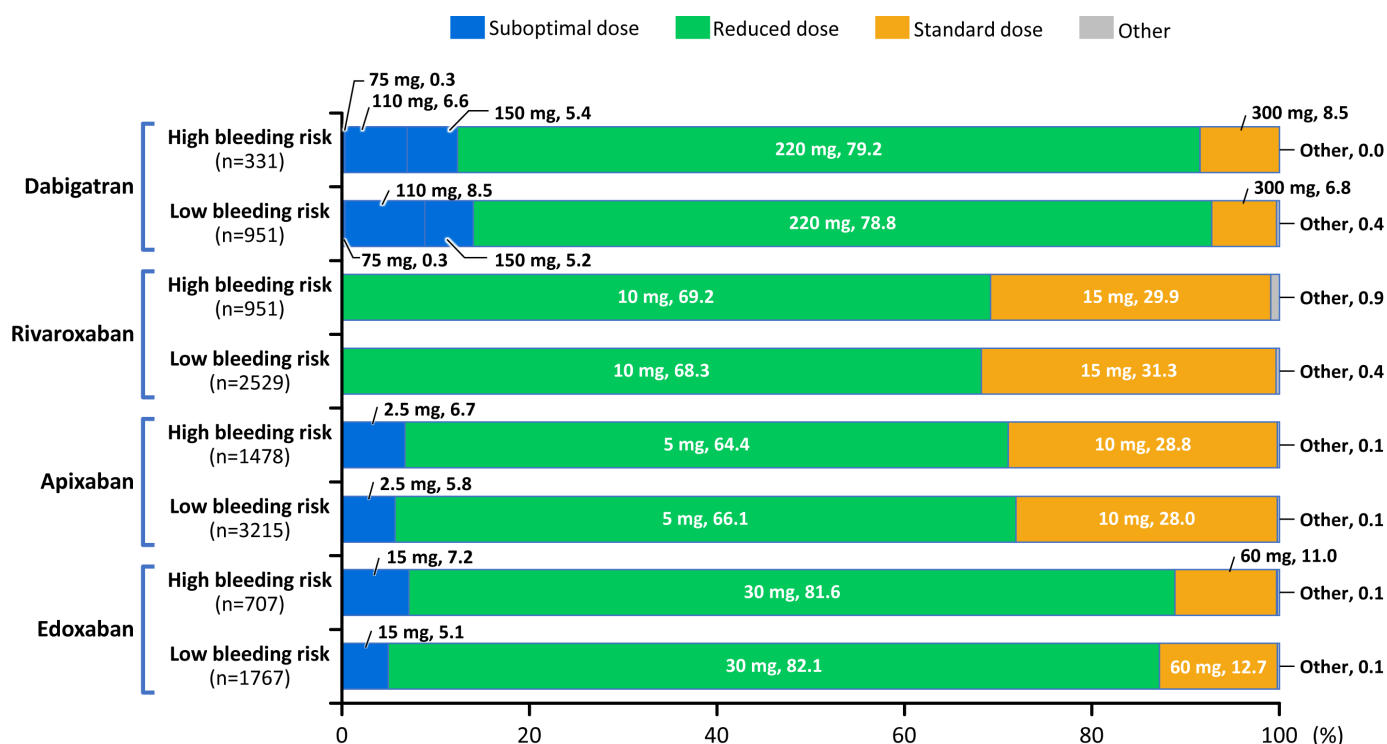
‡Comorbidities were qualified according to the treating physician's judgement.



**Figure 1** Anticoagulant administration classified by bleeding risk<sup>a</sup> in the population at high risk of stroke (CHADS<sub>2</sub> ≥3). In each case, the proportion of patients receiving each type of treatment (warfarin, DOAC, parenteral anticoagulation, or no anticoagulation) is shown. The population of patients receiving DOAC treatment is further categorised according to the specific drug administered (dabigatran, rivaroxaban, apixaban, or edoxaban). <sup>a</sup>High bleeding risk is HAS-BLED ≥3; low bleeding risk is HAS-BLED ≤2. \*P<0.0001 for between-group difference. DOAC, direct oral anticoagulant.



**Figure 2** TTR classified by bleeding risk<sup>a</sup> in the population at high risk of stroke (CHADS<sub>2</sub> ≥3). The TTR indicates the percentage of time a patient’s INR was within the desired treatment range, and was divided into categories of <40%, ≥40% to <60%, ≥60%, or unknown. The proportions of patients within each category are shown. In addition, the category of ≥60% is further divided into ≥60% to <80% and ≥80%. <sup>a</sup>High bleeding risk is HAS-BLED ≥3; low bleeding risk is HAS-BLED ≤2. The overall mean TTR for each group is shown next to the y-axis. For calculation of mean values, unknowns were excluded; thus, <sup>b</sup>n=6966, <sup>c</sup>n=1444, and <sup>d</sup>n=2814. \*p=0.0146 for between-group difference. INR, International Normalized Ratio; TTR, time in therapeutic range.



**Figure 3** DOAC dose distribution classified by bleeding risk<sup>a</sup> in the population at high risk of stroke (CHADS<sub>2</sub> ≥3). The daily dose for each individual DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) was categorised as suboptimal (very low and unlikely to achieve the desired therapeutic effect), reduced (lower than the recommended standard dose, used particularly for elderly patients or special populations), standard (the normal recommended adult dose), or other (eg, suprathreshold doses). The proportions of patients receiving each dose are shown. In addition, as suboptimal dosing (blue bars) may encompass several dosages, each suboptimal dose was noted, and the proportions of patients receiving the specified dose are indicated. <sup>a</sup>High bleeding risk is HAS-BLED ≥3; low bleeding risk is HAS-BLED ≤2. DOAC, direct oral anticoagulant.

rates of kidney disease and bleeding tendency would be higher in the high stroke risk group. This may influence the therapeutic decisions made by the treating physician as some pharmacological agents may not be suitable for use in this population. Indeed, in the high-bleeding risk group, we observed that the prevalence of cerebrovascular disease and CKD was higher and fewer patients received anticoagulant therapy compared with the low bleeding risk group. Moreover, it seems likely that treatment differences between the two groups may be related to the risk assessment factors which differ between the HAS-BLED score and the CHADS<sub>2</sub> score, such as 'renal impairment', 'haemorrhagic disease', and 'poor warfarin management'. Of note, it was unexpected to observe that, among patients with a high risk of stroke and low bleeding risk, the prevalence of heart failure was significantly higher (by 10%) compared with that among patients with high risk of stroke and high bleeding risk. It is difficult to speculate on the reason for this difference, but the higher prevalence of hypertension and diabetes mellitus in the group with lower HAS-BLED scores might have been associated with a higher risk of hypertensive heart disease, diabetic cardiomyopathy, and, by extension, heart failure.

It is well known that kidney disease may be associated with an increased risk of stroke in patients with AF.<sup>17 18</sup> In a health insurance database study of 10 883 patients with AF, the subsequent development of CKD was associated with a 28% greater risk of stroke compared with patients with no CKD.<sup>17</sup> In the GARFIELD-AF registry of 33 024 AF patients, moderate-to-severe CKD was independently associated with a twofold higher risk of stroke/systemic embolism after 1 year of follow-up, relative to patients without CKD.<sup>18</sup> However, the administration of DOACs in patients with renal disease is fraught with difficulty, due to the increased risk of haemorrhage.<sup>19 20</sup> Unfortunately, evidence from clinical trials for the use of DOACs is lacking in AF patients with CKD or end-stage renal disease, and recommendations are conflicting.<sup>21–24</sup> A recent meta-analysis of 16 observation studies evaluated the clinical benefit of DOACs for AF patients on long-term dialysis and concluded that anticoagulation therapy with DOACs in this patient population was not associated with a decreased risk of thrombosis and embolism-related diseases. Further, higher bleeding risk was associated with the use of warfarin, dabigatran and rivaroxaban compared with the use of apixaban and no anticoagulant.<sup>25</sup> Thus, the risk–benefit of DOACs for AF patients with CKD requires further study in randomised controlled trials.

In this analysis, patients with high stroke risk and high bleeding risk had higher rates of renal dysfunction and warfarin use, compared with low bleeding risk patients. It seems likely that warfarin was preferentially prescribed to patients with decreased renal function based on data demonstrating that dose adjustment in patients with AF and CKD could reduce stroke risk.<sup>26</sup> In contrast, DOACs were likely prescribed less often in cases of

renal dysfunction, since they must be used with caution in patients with renal dysfunction defined by creatinine clearance.<sup>5 27 28</sup>

In patients who received DOACs, there were generally no differences in the specific drugs used between bleeding risk groups. However, in line with previous studies,<sup>29–32</sup> many patients were receiving lower than standard doses of DOACs. As published data suggest that increased age alone is not associated with administration of low-dose DOACs,<sup>30 31</sup> we can speculate that clinicians may have prescribed lower than standard doses either because many patients had decreased renal function, or because they were worried about the increased risk of bleeding in these elderly patients.<sup>33–35</sup> Interestingly, the dose distributions were similar, regardless of actual HAS-BLED bleeding risk. This lack of difference in dose distribution was considered to be related to the wide safety range of DOACs. As the blood concentration and effectiveness of a DOAC can be estimated from the dosage administered, dose adjustments can be made according to the dose reduction criteria for each drug rather than being based on patient risk scores.

Overall, our data indicate that in patients with high stroke risk, an accompanying high bleeding risk reduces the likelihood of DOACs being prescribed. For those who do receive DOACs, the dose distribution does not vary markedly from the distribution observed in patients at low bleeding risk. Conversely, patients at high bleeding risk are more likely to be prescribed warfarin and, based on the TTR data, the dose of warfarin is more likely to be reduced. This dichotomy is central to our understanding of the trends in real-world clinical prescribing, and we anticipate that our data will stimulate discussion on current and future treatment paradigms.

Limitations associated with the overall ANAFIE registry have already been reported; these are mainly related to the observational, registry-based design.<sup>13</sup> The fact that the registry was restricted to Japanese patients may also limit the generalisability of the data to patient populations of other races. We also acknowledge that as the CHADS<sub>2</sub> and the HAS-BLED measures both assign scores based on hypertension history, older age, and previous stroke symptoms, the use of these measures to classify patients into risk groups may have introduced an element of selection bias into our analysis. Finally, this study did not consider whether DOAC or warfarin doses were reduced in accordance with the dose reduction criteria for individual drugs or whether they were reduced for other reasons, without meeting the criteria. This is a key point, which will be investigated during the follow-up period of the ANAFIE study, to enable understanding of the impact of unwarranted dose reduction (without meeting the criteria) on event occurrence.

In conclusion, we found that elderly patients with NVAf at high risk of stroke (CHADS<sub>2</sub> score  $\geq 3$ ) and bleeding (HAS-BLED  $\geq 3$ ) had significant demographic and clinical differences compared with patients with low bleeding risk. Administration of low-dose DOACs was frequent in

these elderly NVAf patients, and the dose distribution was not affected by bleeding risk. Because most data related to the bleeding risk of DOACs has been obtained from clinical trials, it is likely that elderly patients aged  $\geq 75$  years with multiple comorbidities and high stroke and bleeding risk scores were excluded. Our data provide insight into real-world clinical anticoagulation use in this population.

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