Original Article
Characteristics of non-valvular atrial fibrillation patients who benefit most from anticoagulation treatment

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Abstract: Objectives: The objective was to determine who will benefit most from oral anticoagulation (OAC) for non-valvular atrial fibrillation (NVAF) patients aged ≥ 75 years. Background: It was unclear whether all of NVAF aged ≥ 75 should receive OAC. Methods: We recruited NVAF ≥ 75 years without QAC who were divided into three groups according to $CHA_2DS-VASc$ scores. The clinical endpoints were ischemic stroke (IS), thromboembolism (TE), or death. Results: The patients with CHA_2DS_2-VASc score of 6-9 were not appropriate for anticoagulation with the highest HAS-BLED scores. CHA_2DS_2-VASc of 2 had little risk for IS/TE. We further divided CHA_2DS_2-VASc of 3-5 into three subgroups with estimated glomerular filtration rate (eGFR; ml/min/1.73 m^2): < 30, 30-60, and > 60. The patients with eGFR < 30 had the highest bleeding risk with a comparable IS/TE. Conclusions: NVAF with CHA_2DS_2-VASc of 3-5 and eGFR > 30 ml/min/1.73 m^2 represent the most appropriate population for anticoagulation.

Keywords: Atrial fibrillation, elderly, CHA_2DS_2-VASc score, eGFR, anticoagulation

Introduction

Atrial fibrillation (AF) is a common arrhythmia that has been shown to be an independent risk factor for stroke and is associated with marked morbidity and mortality [1, 2]. Recently, a newly developed scoring system, the CHA_2DS_2-VASc (congestive heart failure; hypertension; age ≥ 75 years [doubled]; type 2 diabetes; previous stroke, transient ischemic attack, or thromboembolism [doubled]; vascular disease; age 65-75 years; and sex category) score was recommended to guide antithrombotic therapy in patients with AF [3-5]. According to this scoring scheme, all AF patients aged 75 years or older should receive oral anticoagulation (OAC). However, it was unclear whether AF patients aged 75 years or over who exhibited a high risk of stroke without any complications should receive OAC. On the other hand, AF patients with higher CHA_2DS_2-VASc scores also have a higher bleeding risk, which is one of the most important reasons why in China the rate of OAC treatment is very low among non-valvular AF (NVAF) patients aged ≥ 75 years old compared to that among patients < 75 years [6, 7]. In addition, it is well known that impaired kidney function increases the risk of bleeding in elderly NVAF patients. The objective of the present study was to determine whether a specific population of NVAF patients 75 years or older who would experience the highest safety and efficacy from anticoagulation treatment could be screened out based on the CHA_2DS_2-VASc score and kidney function, which was determined by estimated glomerular filtration rate (eGFR).

Methods and materials

Study participants

This retrospective evaluation collected patients' data from January 1, 2011 to June 30, 2013, from Beijing Friendship Hospital (Beijing, China). Linking data to any specified individual patient was possible via a unique and permanent personal registration number. The NVAF patients aged 75 years or over were enrolled in this study. Diagnosis of AF was based on 12-lead electrocardiography (ECG) or 24-hour Holter monitoring results. Patients were excluded if they met one of the following conditions: valvular AF, rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, mitral valve repair, and receiving hemodialysis or any OAC.

Table 1. Comparison of demographic and clinical characteristics of NVAF patients with different CHA_2DS_2-VASc scores

Variable	Patients	CHA_2DS_2-VASc scores			P
		2 (n=7)	3-5 (n=158)	6-9 (n=113)	
Age, years	83.16±4.89	82.57±2.99	82.98±5.21	83.45±4.50	0.71
Female [n (%)]	75 (27%)	4 (57.1%)	36 (22.8%)	35 (31%)	0.062
Heart failure [n (%)]	64 (23%)	0 (0%)	33 (20.9%)	31(27.4%)	0.154
Hypertension [n (%)]	208 (74.8%)	2 (28.6%)	111 (70.3%)*	95 (84.1%)	0.001
Diabetes mellitus [n (%)]	96 (34.5%)	0 (0%)	45 (28.5%)*	51 (45.1%)	0.003
Previous stroke/TIA [n (%)]	118 (42.4%)	0 (0%)	22 (13.9%)*	96 (85%)	0.000
Vascular disease [n (%)]	157 (56.5%)	0 (0%)	76 (48.1%)*	81 (71.7%)	0.000
eGFR (ml/min/1.73 m²)	64.72±23.11	60.29±20.57	62.94±23.81	67.49±22.15	0.246
CHA_2DS_2-VASc	5.00±1.48	2.00	4.06±0.78*	6.50±0.71	0.000
Bleeding [n (%)]	31 (11.2%)	0 (0%)	13 (8.2%)*	18 (15.9%)	0.089
BP > 160 mmHg [n (%)]	26 (9.4%)	1 (14.3%)	12 (7.6%)	13 (11.5%)	0.498
Abnormal liver function [n (%)]	6 (2.2%)	0 (0%)	3 (1.9%)	3 (2.7%)	0.845
Abnormal renal function [n (%)]	15 (5.4%)	1 (14.3%)	10 (6.3%)	4 (3.5%)	0.347
HAS-BLED	2.28±0.86	1.29±0.49	1.96±0.73*	2.80±0.78	0.000
Antiplatelets [n (%)]	182 (65.5%)	5 (71.4%)	96 (60.8%)	81 (71.7%)	0.166

TIA: transient ischemic attack; eGFR: estimated glomerular filtration rate; CHA_2DS_2-VASc: Congestive heart failure; Hypertension, Age 75 years, Diabetes mellitus, previous Stroke, transient ischemic attack, or thromboembolism, Vascular disease, Age 65 to 74 years, Sex category; HAS-BLED: Hypertension, Abnormal renal function (Serum creatinine ≥ 200 μmol/L), abnormal liver function (bilirubin > 2 × upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3 × upper limit normal), Stroke, Bleeding, Labile international normalized ratio, Elderly, Drug therapy, alcohol intake, NSAID nonsteroidal anti-inflammatory drug. *P < 0.05 compared with patients with CHA_2DS_2-VASc scores of 6-9.

Data were collected at baseline and during the follow-up period. The date of each qualifying AF diagnosis between January 1, 2011 and June 30, 2013 was designated as the index date. Data collected during the baseline period, which ended on the index date, were used to obtain information about each patient's medical history. Data collected within the follow-up period, which started the day after the index date and ended on March 1, 2015, were used to assess thrombus risk.

Determination of risk events and endpoints

The primary endpoint was ischemic stroke (IS), thromboembolism (TE; transient ischemic attack [TIA], peripheral embolism), or death. Information about end points was collected from hospital databases.

Stroke was defined as a new and sudden focal neurological deficit resulting from a presumed cerebrovascular cause that persists beyond 24 hours and is not attributed to other identifiable causes such as tumor or seizure. Events that lasted < 24 hours are defined as TIA. Brain imaging was used in each case to distinguish hemorrhagic from ischemic stroke. Peripheral artery embolism was defined as abrupt vascular insufficiency associated with clinical or radiographic evidence of peripheral arterial occlusion in the absence of another likely mechanism.

Our study was a retrospective evaluation, we had not signed consent from patients.

eGFR determination

At study entry, serum creatinine levels were evaluated, and the glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease equation (MDRD): eGFR (ml/min/1.73 m²) = 186 × [serum creatinine (mg/dl)] -1.154 × (age) -0.203 × (0.742 if female) [8].

Statistical analysis

Data are expressed as mean ± standard deviation (SD). All analyses were performed using SPSS 17.0 (SPSS, Inc.). Mean values and proportions of variables were compared using unpaired Student's *t* tests, analysis of variance, and chi-square tests whenever applicable. We constructed receiver operating characteristic
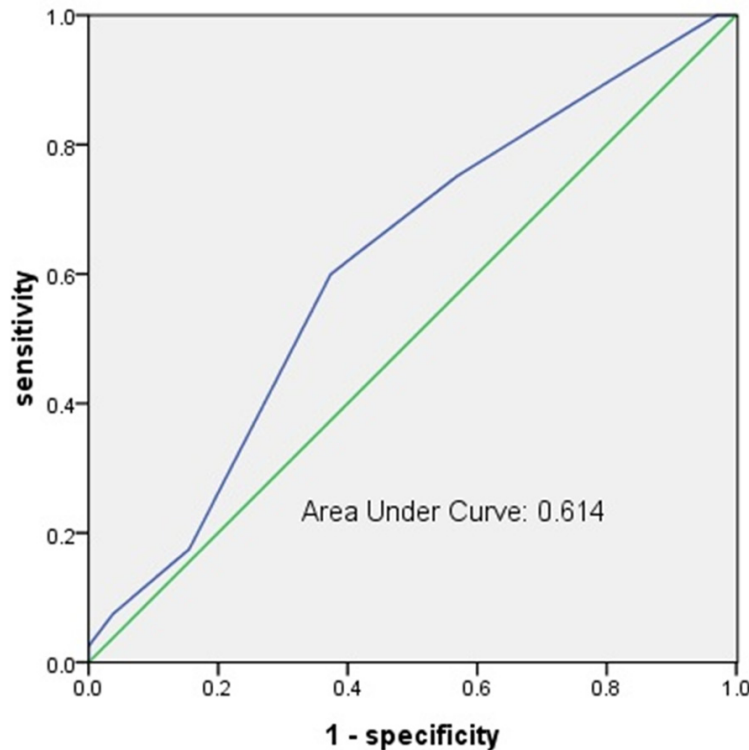
Figure 1. Receiver-operating curves (ROCs) of CHA_2DS_2-VASc scores for IS/TE.

scores, with a cut-off point of 5.5, which presented the highest overall predictive performance (with a sensitivity of 60% and a specificity of 62.6%) for the occurrence of IS/TE.

We divided the patients into three groups based on the CHA_2DS_2-VASc scores: low-risk (CHA_2DS_2-VASc score of 2), intermediate-risk (CHA_2DS_2-VASc score of 3-5), and high-risk (CHA_2DS_2-VASc score of 6-9). **Table 1** lists and compares the clinical characteristics of patients in these three groups. The patients in the low-risk group showed no complications other than age as a risk factor and had no medical history of heart failure, diabetes mellitus, previous stroke/TIA, vascular disease, or bleeding. In addition, their average HAS-BLED score was lower than those of the intermediate-risk and high-risk groups (1.29±0.49 vs. 1.96±0.73 and 2.80±0.78, respectively; P < 0.001). The high-risk group, which was set by the cut-off value of 5.5, had a higher occurrence rate of heart failure, diabetes mellitus, previous stroke/TIA, vascular disease, and bleeding events than did the intermediate-risk group (P < 0.01), and their average HAS-BLED score was also significantly higher than that of the intermediate-risk group (2.80±0.78 vs. 1.96±0.73, P < 0.01).

Consistent with the above data, as shown in the Kaplan-Meier survival analysis (**Figure 2A**), whereas the patients with a CHA_2DS_2-VASc score of 2 showed no IS/TE, the patients with a CHA_2DS_2-VASc score of 6-9 had a higher IS/TE event rate than those in the low- and intermediate-risk groups (21.2% vs. 0% and 10.1%, respectively, P=0.014). Taken together, these results indicate that patients in either the high-risk group, which exhibited a high bleeding risk, or in the low-risk group, which exhibited little risk of IS/TE, were not appropriate candidates for anticoagulation treatment.
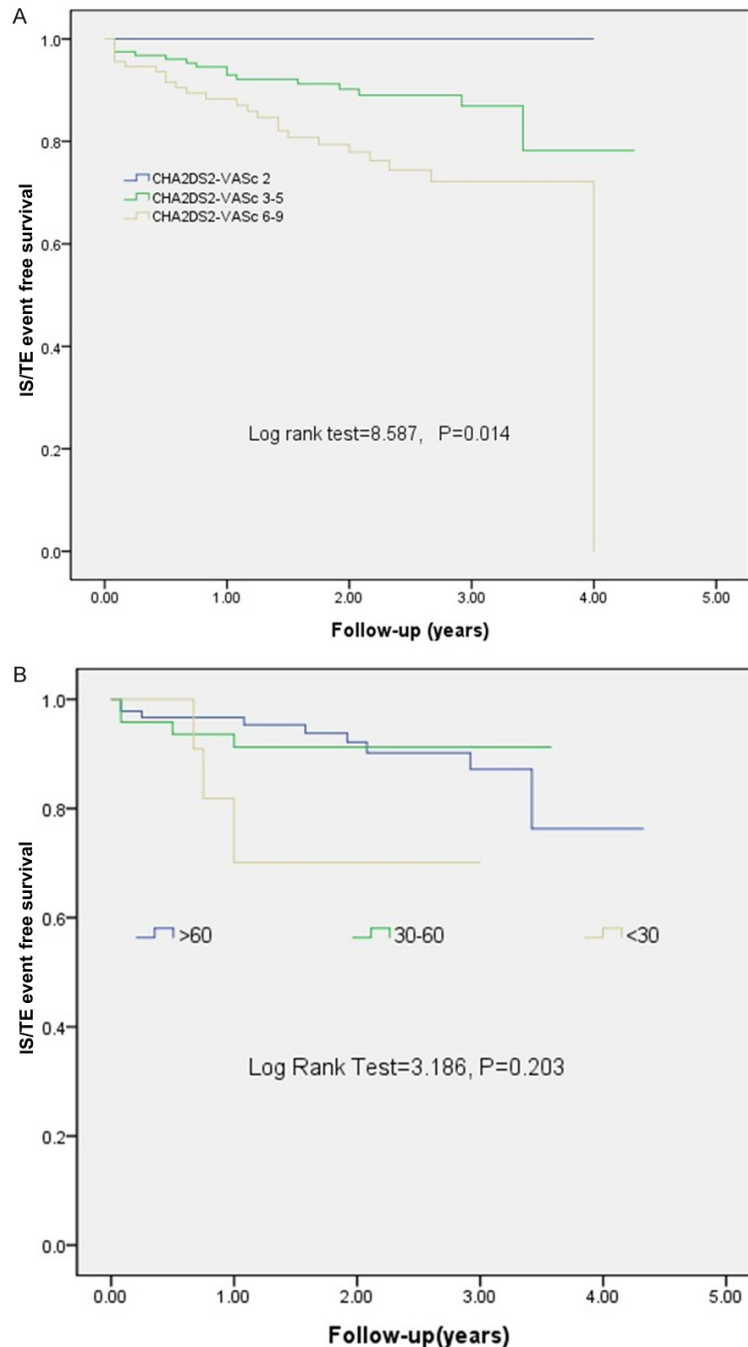
(ROC) curves to identify the cut-off value of CHA_2DS_2-VASc score that predicted the IS/TE risk. The IS/TE risks were displayed with Kaplan-Meier curves and compared using the log-rank test. A *p* value less than 0.05 was considered statistically significant.

Results

Characteristics of the study population

For the present study, we recruited 278 NVAF patients aged 75 years or over. The mean patient age was 83.16±4.89 years, and patients included 75 (27%) females and 203 (73%) males. During a follow-up period of 2.07±1.41 years, 81 patients (23.1%) died and 48 (13.7%) experienced IS/TE. Baseline demographic and clinical characteristics of the patients are shown in **Table 1**.

Association of CHA_2DS_2-VASc scores with adverse events

Figure 1 shows the ROC curves for predicting IS/TE events based on the CHA_2DS_2-VASc

Figure 2. IS/TE event free survival curves for patients with different CHA$_2$DS$_2$-VASc scores and patients with different eGFRs and a CHA$_2$DS$_2$-VASc of 3-5 IS/TE events curves for patients in the different CHA$_2$DS$_2$-VASc score groups (A) or with different eGFRs in the group with CHA$_2$DS$_2$-VASc scores of 3-5 (B).

(10.1%) patients selected according to baseline characteristics were further divided into three subgroups based on the eGFR (< 30, 30-59, and ≥ 60 ml/min/1.73 m^2), a kidney function index (**Table 2**). Individuals with a decreased eGFR were older and had a higher risk of bleeding (as assessed by the HAS-BLED score). Although patients with an eGFR < 30 ml/min/1.73 m^2 had a higher event rate than those with an eGFR of 30-59 or ≥ 60 ml/min/1.73 m^2 (16.7% vs. 8.3% and 9.8%, respectively), the difference was not statistically significant (P=0.583; **Table 2**). Consistent with this, Kaplan-Meier survival analysis showed that the patients with an eGFR < 30 ml/min/1.73 m^2 had no significantly higher adverse event rate compared with other groups after follow-up (Log rank test =3.186, P=0.203; **Figure 2B**). Because the patients in the subgroup with an eGFR < 30 mL/min/1.73 m^2 had a high risk for bleeding but a comparable IS/TE rate in relation to the other two subgroups, anticoagulation treatment should not be recommended for these patients. Thus, we conclude that patients in the subgroups with an eGFR > 30 mL/min/1.73 m^2 should be the most appropriate candidates for anticoagulation treatment.

Discussion

According to the flow chart of the current guidelines of the European Society of Cardiology regarding the use of OACs, chronic OAC therapy should be recommended for all patients ≥ 75 years old with a CHA$_2$DS$_2$-VASc score ≥ 2. However, it was observed that in China, OACs were underused (25.4%), particularly in elderly patients with a high risk of stroke [6]. Doctors

Association of eGFR with risk of adverse events in patients with CHA$_2$DS$_2$-VASc scores of 3-5

The results of analysis of 158 intermediate-risk patients with CHA$_2$DS$_2$-VASc scores of 3-5, 16

Table 2. Comparison of clinical characteristics among different CHA_2DS_2-VASc groups stratified by eGFR

Variables	eGFR (ml/min/1.73 m²)			p
	eGFR ≥ 60 n=92	eGFR 30-60 n=48	eGFR < 30 n=18	
Age, yrs	81.88±4.82	84.08±5.42*	85.33±5.61*	0.007
Female [n (%)]	17 (18.5%)	14 (29.2%)	5 (27.8%)	0.311
Heart failure [n (%)]	16 (17.4%)	11 (22.9%)	6 (33.3%)	0.288
Hypertension [n (%)]	64 (69.6%)	34 (70.8%)	13 (72.2%)	0.969
Diabetes mellitus [n (%)]	27 (29.3%)	13 (27.1%)	5 (27.8%)	0.959
Previous stroke/TIA [n (%)]	16 (17.4%)	6 (12.5%)	1 (5.6%)	0.381
Vascular disease [n (%)]	44 (47.8%)	25 (52.1%)	7 (38.9%)	0.631
CHA_2DS_2-VASc	4.10±0.77	4.08±0.79	3.83±0.86	0.421
Bleeding [n (%)]	9 (9.8%)	4 (8.3%)	1 (5.6%)	0.837
BP ≥ 160 mmHg [n (%)]	6 (6.5%)	4 (8.3%)	2 (11.1%)	0.777
eGFR (ml/min/1.73 m²)	79.66±11.72	47.41±8.03*	18.89±8.61*	0.036
Abnormal liver function [n (%)]	2 (2.2%)	1 (2.1%)	0 (0%)	0.821
Abnormal renal function [n (%)]	0 (0%)#	0 (0%)#	10 (55.6%)	0.000
Antiplatelts [n (%)]	57 (62%)	26 (54.2%)	13 (72.2%)	0.382
HAS-BLED ≥ 3 [n (%)]	16 (17.4%)#	5 (10.4%)#	6 (33.3%)	0.048
IS/TE rate [n (%)]	9 (9.8%)	4 (8.3%)	3 (16.7%)	0.598

*P < 0.05 compared with patients with an eGFR ≥ 60 ml/min/1.73 m². #P < 0.05 compared with patients with an eGFR < 30 ml/min/1.73 m².

were concerned about bleeding risk, especially intracerebral hemorrhage caused by OAC. Partington et al [4, 5] found that advanced age was the strongest predictor of warfarin non-use, especially in patients ≥ 75 years. Therefore, it is necessary to select a more appropriate subgroup of NVAF patients to receive OAC treatment to benefit more patients and increase the OAC treatment rate. The main findings of the present study were as follows: CHA_2DS_2-VASc scores were useful parameters for predicting adverse events in NVAF patients aged 75 years or over with a cut-off value of 5.5. The patient with a CHA_2DS_2-VASc score of 3-5 had a lower bleeding risk and higher IS risk, and thus were designated as the intermediate-risk group. However, OAC treatment was not appropriate for all patients in the intermediate-risk group, because those patients with significantly impaired kidney function, as indicated by an eGFR < 30 ml/min/1.73 m², had a higher bleeding risk without any increased IS/TE risk. Thus, our study suggested that NVAF patients with a CHA_2DS_2-VASc score of 3-5 and an eGFR ≥ 30 ml/min/1.73 m² represented the most appropriate subgroup to receive anticoagulation treatment based on the expected benefit.

A cut-off point for the CHA_2DS_2-VASc score of 5.5 was associated with the highest sensitivity and specificity for the occurrence of IS/TE, suggesting that a CHA_2DS_2-VASc score ≥ 6 could be used to refine stroke risk stratification in AF patients aged 75 years or over. Of note, patients with a CHA_2DS_2-VASc score of 2 with no morbidity also had no IS/TE events. It appeared that that stroke risk was low in this subgroup of patients, and anticoagulation treatment was not needed for them. A CHA_2DS_2-VASc score of ≥ 6 was associated with an approximate 2.0-fold increase in the IS/TE risk compared to a score of 3-5, which also was associated with a higher bleeding risk as indicated by a HAS-BLED score of 2.8. Thus, the patients in this group appeared not to be appropriate candidates for anticoagulation treatment. Solely based on the CHA_2DS_2-VASc scoring system, it seemed that anticoagulation treatment for patients with a CHA_2DS_2-VASc score of 3-5 had a significant net clinical benefit, because these patients had a lower risk of bleeding and higher risk of stroke.

Because impaired kidney function may increase the risk of bleeding, in the present study, we assessed the eGFR of patients with CHA_2DS_2-

VASc scores of 3-5, and further divided them into three subgroups: eGFR $\geq$ 60 ml/min/1.73 m^2, eGFR =30-60 ml/min/1.73 m^2, and eGFR < 30 ml/min/1.73 m^2 (mean eGFRs =79.66 ml/min 1.73 m^2, 47.41 ml/min/1.73 m^2, and 18.89 ml/min/1.73m^2. respectively). Patients with an eGFR < 30 ml/min/1.73 m^2 had the highest HAS-BLED scores without a significant increase in the occurrence of IS/TE events compared with those in the other two subgroups, while the patients in the other two subgroups showed no significant differences in either HAS-BLED score or risk of IS/TE. Therefore, of patients 75 years of age or over, anticoagulation treatment may be most efficient and safest among those with a CHADSc-VASc score of 3-5 and an eGFR > 30 ml/min/1.73 m^2. Compared with the patients in other groups.

The association between chronic kidney disease (CKD) and AF has been previously studied [8-14]. Most studies report that CKD can increase the risk of TE in patients with AF [5-9]. However, no significant increase in the occurrence rate of stroke/TE was observed in the intermediate-risk group compared with the other two groups. This was likely because the patients with CHA$_2$DS$_2$-VASc score of 3-5 had only one to three risk factors other than advanced age, and the variation range of scores was not large. This suggested that risk factors other than CKD had a major effect on stroke in AF patients. Our results were consistent with those of several previous reports [15, 16]. For example, Roldán et al studied 978 patients with a median age of 76 years and found that 31% had an eGFR < 30 ml/min/1.73 m^2. They added 1 point to the CHA$_2$DS$_2$-VASc scores if the eGFR was 30-60 ml/min/1.73 m^2 and 2 points if the eGFR was < 30 ml/min /1.73 m^2 and found that CKD did not independently improve the predictive ability of the CHA$_2$DS$_2$-VASc scores for thromboembolic events and mortality [15]. Similar results were obtained by another group when an eGFR of < 60 ml/min/1.73 m^2 (one point or two points) was added in the calculation of the CHA$_2$DS$_2$-VASc score [16]. Given that renal impairment is commonly associated with the stroke risk factors listed within the CHA$_2$DS$_2$-VASc scores, the lack of an independent additive predictive value may perhaps be unsurprising.

In conclusion, NVAF patients with an age of 75 years or over, a CHA$_2$DS$_2$-VASc score of 3-5, and

an eGFR $\geq$ 30 ml/min/1.73 m^2 represent the most appropriate group of patients for anticoagulation treatment, which will reduce the risk of bleeding and yield considerable clinical benefits.

Limitations

Some limitations need to be noted in the present study. First, this was a single medical center survey. Second, the sample size was relatively small. Particularly, the number of patients in the group with a CHA$_2$DS$_2$-VASc score of 2 was much fewer than those in the other two groups. Also, the overall eGFR level was high even in the group of patients with a CHA$_2$DS$_2$-VASc score of 6-9. In addition, we only assessed the bleeding risk using HAS-BLED scores and did not consider real bleeding events linked to anticoagulation treatment. Thus, future large-scale studies involving multiple centers are needed to further corroborate our findings.

Acknowledgements

Disclosure of conflict of interest

None.

Abbreviations

OAC, oral anticoagulation; NVAF, Non-valvular atrial fibrillation; eGFR, estimated glomerular filtration rate; IS, Ischemic stroke; TE, Thromboembolism; CHA$_2$DS$_2$-VASc, congestive heart failure; hypertension; age $\geq$ 75 years [doubled]; type 2 diabetes; previous stroke, transient ischemic attack, or thromboembolism [doubled]; vascular disease; age 65-75 years; and sex category; ECG, electrocardiography; TIA, transient ischemic attack; MDRD, Modification of Diet in Renal Disease equation; ROC, receiver operating characteristic; HAS-BLED, Hypertension, Abnormal renal function (Serum creatinine $\geq$ 200 µmol/L), abnormal liver function (bilirubin > 2 × upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3 × upper limit normal), Stroke, Bleeding, Labile international normalized ratio,

Elderly, Drug therapy, alcohol intake; CKD, chronic kidney disease.

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