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ORIGINAL ARTICLE

Net clinical benefit of oral anticoagulants in Korean atrial fibrillation patients with low to intermediate stroke risk: A report from the Clinical Survey on Stroke Prevention in patients with Atrial Fibrillation (CS-SPAF)

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Abstract

Background: The balance of stroke risk reduction and potential bleeding risk associated with antithrombotic treatment (ATT) remains unclear in atrial fibrillation (AF) at non-gender CHA_2DS_2-VASc scores 0–1. A net clinical benefit (NCB) analysis of ATT may guide stroke prevention strategies in AF with non-gender CHA_2DS_2-VASc scores 0–1.

Methods: This multi-center cohort study evaluated the clinical outcomes of treatment with a single antiplatelet (SAPT), vitamin K antagonist (VKA), and non-VKA oral anticoagulant (NOAC) in non-gender CHA_2DS_2-VASc score 0–1 and further stratified by biomarker-based ABCD score (Age [≥60 years], B-type natriuretic peptide [BNP] or N-terminal pro-BNP [≥300 pg/mL], creatinine clearance [<50 mL/min], and dimension of the left atrium [≥45 mm]). The primary outcome was the NCB of ATT, including composite thrombotic events (ischemic stroke, systemic embolism, and myocardial infarction) and major bleeding events.

Results: We included 2465 patients (age 56.2 ± 9.5 years; female 27.0%) followed-up for 4.0 ± 2.8 years, of whom 661 (26.8%) were treated with SAPT; 423 (17.2%) with VKA; and 1040 (42.2%) with NOAC. With detailed risk stratification using the ABCD score, NOAC showed a significant positive NCB compared with the other ATTs (SAPT vs. NOAC, NCB 2.01, 95% confidence interval [CI] 0.37–4.66; VKA vs. NOAC, NCB 2.38, 95% CI 0.56–5.40) in ABCD score ≥1. ATT failed to show a positive NCB in patients with truly low stroke risk (ABCD score = 0).

Conclusions: In the Korean AF cohort at non-gender CHA_2DS_2-VASc scores 0–1, NOAC showed significant NCB advantages over VKA or SAPT with ABCD score ≥1.

KEYWORDS
ABCD score, antithrombotic treatment, atrial fibrillation, net clinical benefit, non-vitamin K antagonist oral anticoagulant

1 | INTRODUCTION

Atrial fibrillation (AF) increases the risk of stroke and thromboembolism more than fivefold compared to non-AF populations[1] and AF-related stroke accompanies a higher mortality, morbidity,[2] and healthcare cost.[3] Stroke prevention is the key to AF management, and many studies have focused on how best to determine which patients should receive anti-thrombotic therapy (ATT) to reduce stroke risk.

The risk of stroke is not homogeneous and depends on various risk factors.[4,5] The score measuring congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, and female gender category (CHA_2DS_2-VASc score) is the risk stratification scheme widely adopted in many guidelines, and this score is useful in distinguishing the low-risk group that does not require ATT (non-gender CHA_2DS_2-VASc score of 0).[6–8] For AF patients with a 'low to intermediate risk' of stroke with a non-gender CHA_2DS_2-VASc score of 0 or 1, the score measuring age ≥60 years, B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) level ≥300 pg/mL, creatinine clearance <50 mL/min, and dimension of the left atrium (LA) ≥ 45 mm (ABCD score) was proposed as an additional biomarker reflecting biological/anatomical status associated with the integrated thrombogenicity of an individual AF patient, and it is useful to distinguish patients in need of ATT.[9]

ATT to prevent ischemic stroke should always be balanced with the potential bleeding risk accompanied by ATT. A few studies have attempted to investigate the net clinical benefit (NCB) between the antithrombotic effect on stroke prevention and the risk of bleeding, including intracranial hemorrhage and major bleeding.[10–12] This NCB approach has been used in previous clinical cohort studies by Connolly et al., Eikelboom et al., and Lip et al.[13–15]

Since the non-negligible stroke risk is as high as 1.51%–2.52%/year in AF with low to intermediate stroke risk, the latest guidelines recommended ATT to those patients according to their individualized stroke risk and NCB.[6–8] Therefore, we evaluated the NCB of ATT in AF patients with low to intermediate stroke risk in combination with the biomarker-based ABCD score.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This study was conducted between January 1, 2010, and December 31, 2019, with a multicenter retrospective cohort design. Patients diagnosed with nonvalvular AF were enrolled in 13 Korean tertiary institutions. Among patients who had no previous history of stroke, transient ischemic attack (TIA), or systemic embolism, adults with low to intermediate stroke risk (non-gender CHA_2DS_2-VASc score of 0 or 1) over 18 years of age were included. Patients receiving anticoagulant therapy for reasons other than AF, such as the presence of mechanical valves and pulmonary embolism or deep vein thrombosis, patients with moderate to severe mitral stenosis, and patients who underwent mitral valve replacement were excluded. In addition, patients receiving a combination of two or more ATTs were excluded. The non-gender CHA_2DS_2-VASc score was calculated as two points for ≥75 years of age, stroke, and TIA; it was also calculated as one point for a history of congestive heart failure or left ventricular ejection fraction less than 40%, hypertension, age 65–74 years, diabetes, history of myocardial infarction (MI), peripheral arterial disease, and aortic plaque.[4,16] For the ABCD scoring for detailed stroke risk stratification, age ≥60 years, BNP or N-terminal pro-BNP (NT-proBNP) level ≥300 pg/mL, creatinine clearance <50 mL/min, and dimension of the LA ≥ 45 mm were calculated as one point (range, 0–4 points).[9] Creatinine clearance was calculated using the Cockcroft–Gault formula,[17] and the LA dimension was measured in the M-mode of the parasternal long axis view of transthoracic echocardiography.[18] According to the stratification method of thromboembolic risk in a previous study, the patients were categorized into two groups according to ABCD score and analyzed as follows: (1) ABCD score 0 and (2) ABCD score ≥1.[19] Patients enrolled in the study were further categorized based on types of ATT as follows: (1) aspirin or P2Y12 inhibitor (clopidogrel) as a single antiplatelet (SAPT) therapy, (2) vitamin K antagonist (VKA) therapy, and (3) non-vitamin K antagonist oral anticoagulant (NOAC) therapy (apixaban, dabigatran, rivaroxaban, or edoxaban).

2.2 | Diagnosis of AF, composite thrombotic events, and major bleeding events

The diagnosis of AF was made based on documentation of 12 lead electrocardiograms (ECGs), which showed a typical pattern of AF with an AF episode duration >30 s, whether asymptomatic or symptomatic.[7,20] Episodes detected by wearable monitors or heart-implanted electronics were not included in the diagnosis of AF. Composite thrombotic events (TEs) were defined as cardioembolic stroke, systemic embolism, and MI. Cardioembolic stroke was diagnosed by neurologists at each institution through TOAST criteria,[21] and systemic embolism events occurring in other organs and MI events were also confirmed by physicians at each institution. Bleeding events were classified as major bleeding according to the International Society on Thrombosis and Haemostasis scale when there was an intracranial hemorrhage (ICH), a decrease in Hb of 2 or more, or a blood transfusion was required.[2,22] All clinically significant events were adjudicated by physicians at each institution.

2.3 | Statistical method

Continuous variables with a normal distribution were expressed as mean and standard deviation, and categorical variables were expressed as numbers and percentages. Nonparametrically distributed data were reported as interquartile ranges and medians. For comparison between groups, continuous variables were compared using a Student's *t*-test or analysis of variance for each case, and categorical variables were analyzed using a chi-squared test or Fisher's exact test as appropriate.

The treatment effect was analyzed as intention-to-treat. Person-year was censored at events of AF ablation, death, end of study observation (December 31, 2019), and change of ATT. The incidence of thrombotic and hemorrhagic events was calculated as the number of events per 100 person-years (P-Y). To adjust for demographic differences in each treatment group, the NCB was calculated for the no-treatment, SAPT, VKA, and NOAC groups, and was stratified by non-gender CHA_2DS_2-VASc and ABCD scores. For the survival analysis in each stratified treatment group, a Kaplan–Meier analysis and Log-rank test were performed.

NCB was calculated as the sum of weighted rate differences using the following equation:

$$\begin{aligned} NCB &= Rate_{\text{not treated}} - Rate_{\text{treated}}: \\ Rate &= w_1 \, X \, R_{\text{ischemic stroke}} \\ &+ w_2 \, X \, R_{ICH} + w_3 \, X \, R_{\text{major bleeding}} + w_4 \, X \, R_{MI} \end{aligned}$$

where major bleeding indicated major extracranial bleeding.[13–15] For example, when estimating the NCB of NOAC in comparison with no ATT, the NCB is given as:

$$NCB = Rate_{\text{No ATT}} - Rate_{NOAC}.$$

If NCB has a positive value, NOAC is preferred over no ATT, and if it has a negative value, no ATT is preferred over NOAC.

Weights were derived from the hazard ratio (HR) of post-event death to HR of death after thrombotic and hemorrhagic events shown in previous registry studies. Based on a Danish cohort in a study by Lip et al., weight was calculated as $w_1 = 1$, $w_2 = 1.82$, $w_3 = 0.71$, and $w_4 = 0.89$.[15] Based on the study by Connolly et al., weight was calculated as $w_1 = 1$, $w_2 = 3.08$, $w_3 = 0.67$, and $w_4 = 0.95$.[13,23] In Eikelboom et al., weight was calculated as $w_1 = 1$, $w_2 = 3.23$, $w_3 = 0.63$, and $w_4 = 0.89$.[14,24] The NCB was calculated for each weight. The 95% confidence interval (CI) of the NCB was expressed by the Skellam distribution, indicating the difference in the Poisson distribution, and was estimated by the Wald test CI.[25]

p-values <.05 were considered statistically significant. All statistical analyses were performed using R version 4.1.3 (Foundation for the Statistical Computing).

2.4 | Ethics statement

This study was approved by the institutional review board of each institution. The authors declare that all supporting data are available within the article. The committee waived written informed consent for each patient due to the retrospective cohort study design. All procedures performed in this study, including human participants, complied with the ethical standards of the institutions and national research committees.

3 | RESULTS

In this study, among 3543 AF patients with various risk factors, 2465 AF patients (mean age 56.2 ± 9.5 years, female 27.3%) with a non-gender CHA_2DS_2-VASc score of 0–1 and an ABCD score of 0–4 were included and followed-up for 4.0 ± 2.8 years (Figure 1). Among these patients, 1037 (42.1%) had a non-gender CHA_2DS_2-VASc score of 0 and 1428 (57.9%) had a non-gender CHA_2DS_2-VASc score of 1. Among all patients, 786 (31.9%) had an ABCD score of 0 and 1679 (68.1%) had an ABCD score of 1 or more. When we classified the patients according to ATT, the largest number of patients with a non-gender CHA_2DS_2-VASc score of 0–1 were treated with NOAC (1040, 42.2%). Only 341 (13.8%) patients were not receiving any ATT, and these patients were younger than those receiving ATT (No ATT, 51.2 ± 10.8 years; SAPT, 54.7 ± 9.3 years; VKA 56.2 ± 9.5 years; NOAC, 58.7 ± 8.7 years, $p < .001$) (Table 1). Only 24 patients (3.6%) receiving SAPT with a non-gender CHA_2DS_2-VASc score of 0 or 1 had vascular disease, previous MI, or peripheral artery disease. Most of the patients taking SAPT had hypertension (30.3%). In addition, most patients not receiving ATT had a non-gender CHA_2DS_2-VASc score of 0 or an ABCD score of 0 (Table 1).

In this study, 72 composite TEs occurred (Table 2). As expected, the absolute incidence of composite TEs was higher in patients with one or more risk factors, regardless of the non-gender CHA_2DS_2-VASc score or ABCD score. Patients not receiving ATT tended to have a higher incidence of composite TEs than those receiving ATT, and patients treated with NOAC showed the lowest incidence of composite TEs (No ATT, 1.01 events/100 P-Y, 95% CI 0.52–1.76; SAPT, 0.75 events/100 P-Y, 95% CI 0.47–1.13; VKA 1.13 events/100 P-Y, 95% CI 0.70–1.73; NOAC, 0.44 events/100 P-Y, 95% CI 0.26–0.71) (Table S1). This trend was maintained even when composite thrombotic risk was stratified by ABCD score (Table 2). Also, the higher risk group with a non-gender CHA_2DS_2-VASc score of 1 and ABCD score ≥1 showed a higher incidence of composite TEs compared to the lower risk group with a non-gender CHA_2DS_2-VASc score of 0 and ABCD score 0 (No ATT, 0.60 events/100 P-Y vs. 1.71 events/100 P-Y; SAPT, 0.00 events/100 P-Y vs. 1.56 events/100

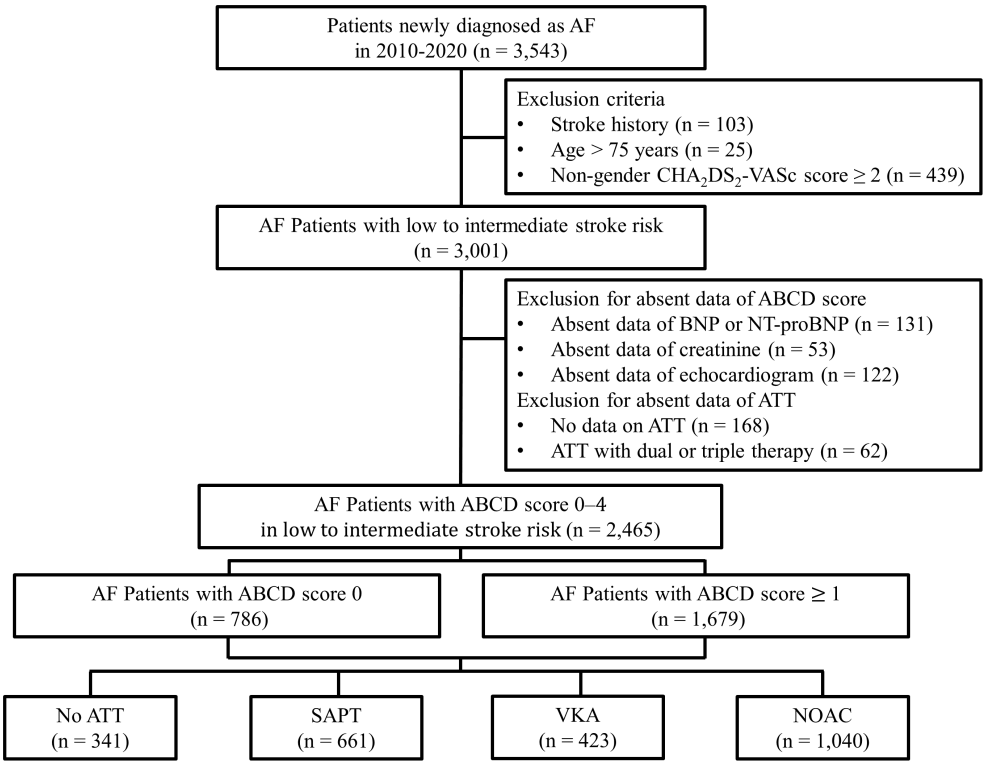

FIGURE 1 Flowchart of the study population for calculating net clinical benefit amongst atrial fibrillation patients with non-gender CHA_2DS_2-VASc scores 0–1 after incident atrial fibrillation. AF indicates atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke or transient ischemic attack (2 points), vascular disease, age 65–74 years, female gender category; ABCD, age ≥ 60 years, BNP level ≥ 300 pg/mL or NT-proBNP level ≥ 300 pg/mL, creatinine clearance <50 mL/min, dimension of the left atrium ≥45 mm; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ATT, antithrombotic therapy; SAPT, single antiplatelet; VKA, vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant.

TABLE 1 Baseline Characteristics in Atrial Fibrillation Patients with Non-gender CHA_2DS_2-VASc scores 0–1.

	No ATT (*N* = 341)	SAPT (*N* = 661)	VKA (*N* = 423)	NOAC (*N* = 1040)	*p*-value
Age (years)	51.2 ± 10.8	54.7 ± 9.3	56.5 ± 8.7	58.7 ± 8.7	<.001
Age ≥ 65 years, *n* (%)	27 (7.9%)	73 (11.0%)	63 (14.9%)	224 (21.5%)	<.001
Gender, *n* (%)					
Female	95 (27.9)	139 (21.0)	84 (19.9)	347 (33.4)	<.001
Male	246 (72.1)	522 (79.0)	339 (80.1)	693 (66.6)	
Hypertension, *n* (%)	81 (23.8)	200 (30.3)	118 (27.9)	324 (31.2)	.058
Diabetes mellitus, *n* (%)	11 (3.2)	24 (3.6)	17 (4.0)	51 (4.9)	.447
Congestive heart failure, *n* (%)	9 (2.6)	33 (5.0%)	46 (10.9%)	97 (9.3%)	<.001
NYHA Class, *n* (%)					
Class I	337 (98.8)	636 (96.2)	385 (91.0)	961 (92.4)	.158
Class II	3 (0.9)	12 (1.8)	15 (3.5)	44 (4.2)	
Class III	1 (0.3)	10 (1.5)	13 (3.1)	19 (1.8)	
Class IV	0 (0.0)	3 (0.5)	10 (2.4)	16 (1.5)	
Vascular disease, *n* (%)	6 (1.8)	14 (2.1)	2 (0.5)	8 (0.8)	.030
Previous MI, *n* (%)	2 (0.6)	7 (1.1)	1 (0.2)	1 (0.1)	.029
Peripheral artery disease	0 (0.0%)	3 (0.5%)	1 (0.2%)	4 (0.4%)	.644
Non-gender CHA_2DS_2-VASc score, *n* (%)					
0 point	207 (60.7)	317 (48.0)	177 (41.8)	336 (32.3)	<.001
1 point	134 (39.3)	344 (52.0)	246 (58.2)	704 (67.7)	
ABCD score, *n* (%)					
0 point	192 (56.3)	282 (42.7)	92 (21.7)	220 (21.2)	<.001
≥1 point	149 (43.7)	379 (57.3)	331 (78.3)	820 (78.8)	
A: Age ≥ 60 years	82 (24.0%)	225 (34.0%)	179 (42.3%)	556 (53.5%)	<.001
B: BNP or NT-proBNP ≥300 pg/mL	30 (8.8%)	75 (11.3%)	84 (19.9%)	154 (14.8%)	<.001
NT-proBNP ≥300 pg/mL	11 (28.9%)	51 (41.8%)	52 (52.0%)	94 (54.7%)	.011
BNP ≥300 pg/mL	19 (11.7%)	25 (11.7%)	33 (20.4%)	64 (19.9%)	.014
C: CrCl <50 mL/min	12 (3.6%)	17 (2.7%)	24 (6.0%)	49 (5.1%)	.037
D: Dimension of LA ≥45 mm	72 (22.2%)	202 (32.2%)	208 (53.6%)	427 (46.7%)	<.001
Follow-up period (years)	3.5 ± 2.6	4.4 ± 2.9	4.4 ± 3.0	3.7 ± 2.7	<.001

Abbreviations: ABCD, Age ≥ 60 years, BNP level ≥ 300 pg/mL or NT-proBNP level ≥ 300 pg/mL, Creatinine clearance <50 mL/min, Dimension of the left atrium ≥45 mm; ATT indicates antithrombotic therapy; BNP, B-type natriuretic peptide; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, prior Stroke or transient ischemic attack (2 points), Vascular disease, Age 65–74 years, female gender category; CrCl, creatinine clearance; LA, left atrium; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SAPT, single anti-platelet; VKA, vitamin K antagonist.

P-Y; VKA, 0.69 events/100 P-Y vs. 1.45 events/100 P-Y; NOAC, 0.50 events/100 P-Y vs. 0.32 events/100 P-Y).

During the follow-up period, a total of 36 cases of major bleeding occurred, including ICH (Table 3). The overall major bleeding incidence was the lowest in patients without ATT and the highest in patients receiving VKA therapy (No ATT, 0.09 events/100 P-Y, 95% CI 0.00–0.48; SAPT, 0.45 events/100 P-Y, 95% CI 0.24–0.77; VKA 1.06 events/100 P-Y, 95% CI 0.65–1.64; NOAC, 0.05 events/100 P-Y, 95% CI 0.01–0.18). ICH did not occur in any patients who had no ATT and was the most prevalent in patients receiving VKA (SAPT,

TABLE 2 Incidence of composite thrombotic events according to ABCD and non-gender CHA_2DS_2-VASc scores.

		No ATT (*N* = 341)			SAPT (*N* = 661)			VKA (*N* = 423)			NOAC (*N* = 1040)		
		N	Event	Incidence rate (95% CI), 100 person-years	*N*	Event	Incidence rate (95% CI), 100 person-years	*N*	Event	Incidence rate (95% CI), 100 person-years	*N*	Event	Incidence rate (95% CI), 100 person-years
Composite thrombotic event													
Non-gender CHA_2DS_2-VASc score	ABCD score												
0	0	140	3	0.60 (0.12–1.74)	172	0	0.00 (0.00–0.52)	55	2	0.69 (0.08–2.48)	116	2	0.50 (0.06–1.79)
0	≥1	67	3	1.34 (0.28–3.92)	145	4	0.61 (0.17–1.57)	122	5	1.00 (0.32–2.33)	220	6	0.70 (0.26–1.52)
1	0	52	1	0.58 (0.01–3.26)	110	2	0.36 (0.04–1.30)	37	1	0.62 (0.02–3.44)	104	2	0.53 (0.06–1.91)
1	≥1	82	5	1.71 (0.55–3.98)	234	16	1.56 (0.89–2.54)	209	13	1.45 (0.77–2.48)	600	7	0.32 (0.13–0.65)
Ischemic stroke and systemic embolism													
Non-gender CHA_2DS_2-VASc score	ABCD score												
0	0	140	2	0.40 (0.05–1.44)	172	0	0.00 (0.00–0.52)	55	2	0.69 (0.08–2.48)	116	2	0.50 (0.06–1.79)
0	≥1	67	1	0.45 (0.01–2.49)	145	2	0.31 (0.04–1.11)	122	4	0.80 (0.22–2.04)	220	4	0.47 (0.13–1.19)
1	0	52	0	0.00 (0.00–2.16)	110	1	0.18 (0.00–1.01)	37	1	0.62 (0.02–3.44)	104	1	0.26 (0.01–1.47)
1	≥1	82	4	1.37 (0.37–3.50)	234	10	0.98 (0.47–1.80)	209	10	1.12 (0.54–2.05)	600	5	0.23 (0.07–0.53)
Myocardial infarction													
Non-gender CHA_2DS_2-VASc score	ABCD score												
0	0	140	1	0.20 (0.01–1.11)	172	0	0.00 (0.00–0.52)	55	0	0.00 (0.00–1.27)	116	0	0.00 (0.00–0.91)
0	≥1	67	2	0.89 (0.11–3.23)	145	2	0.31 (0.04–1.11)	122	1	0.20 (0.01–1.11)	220	2	0.23 (0.03–0.84)
1	0	52	1	0.58 (0.01–3.26)	110	1	0.18 (0.00–1.01)	37	0	0.00 (0.00–2.28)	104	1	0.26 (0.01–1.47)
1	≥1	82	1	0.34 (0.01–1.90)	234	6	0.59 (0.22–1.28)	209	3	0.34 (0.07–0.98)	600	2	0.09 (0.01–0.33)

Abbreviations: ABCD, Age ≥60 years, BNP level ≥ 300 pg/mL or NT-proBNP level ≥ 300 pg/mL, Creatinine clearance <50 mL/min, Dimension of the left atrium ≥45 mm; ATT, antithrombotic therapy; BNP, B-type natriuretic peptide; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 (2 points), Diabetes mellitus, prior Stroke or transient ischemic attack (2 points), Vascular disease, Age 65–74 years, female gender category; CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAPT, single anti-platelet; VKA, vitamin K antagonist.

TABLE 3 Incidence of major bleeding events according to ABCD and non-gender CHA_2DS_2-VASc scores.

		No ATT (*N* = 341)			SAPT (*N* = 661)			VKA (*N* = 423)			NOAC (*N* = 1040)		
		N	Event	Incidence rate (95% CI), 100 person-years	*N*	Event	Incidence rate (95% CI), 100 person-years	*N*	Event	Incidence rate (95% CI), 100 person-years	*N*	Event	Incidence rate (95% CI), 100 person-years
Total major bleeding event													
Non-gender CHA_2DS_2-VASc score	ABCD score												
0	0	140	0	0.00 (0.00–0.74)	172	1	0.14 (0.00–0.79)	55	2	0.69 (0.08–2.49)	116	0	0.00 (0.00–0.88)
0	≥1	67	0	0.00 (0.00–1.79)	145	4	0.61 (0.17–1.56)	122	5	0.97 (0.32–2.27)	220	1	0.11 (0.00–0.64)
1	0	52	0	0.00 (0.00–2.16)	110	1	0.18 (0.00–1.03)	37	5	2.90 (0.94–6.77)	104	0	0.00 (0.00–1.00)
1	≥1	82	1	0.35 (0.01–1.97)	234	7	0.70 (0.28–1.45)	209	8	0.88 (0.38–1.74)	600	1	0.04 (0.00–0.25)
ICH													
Non-gender CHA_2DS_2-VASc score	ABCD score												
0	0	140	0	0.00 (0.00–0.74)	172	0	0.00 (0.00–0.52)	55	1	0.34 (0.01–1.92)	116	0	0.00 (0.00–0.88)
0	≥1	67	0	0.00 (0.00–1.79)	145	2	0.31 (0.04–1.10)	122	1	0.19 (0.00–1.08)	220	1	0.11 (0.00–0.64)
1	0	52	0	0.00 (0.00–2.16)	110	0	0.00 (0.00–0.68)	37	0	0.00 (0.00–2.14)	104	0	0.00 (0.00–1.00)
1	≥1	82	0	0.00 (0.00–1.31)	234	2	0.20 (0.02–0.73)	209	3	0.33 (0.07–0.97)	600	1	0.04 (0.00–0.25)
Major bleeding event (except ICH)													
Non-gender CHA_2DS_2-VASc score	ABCD score												
0	0	140	0	0.00 (0.00–0.74)	172	1	0.14 (0.00–0.79)	55	1	0.34 (0.01–1.92)	116	0	0.00 (0.00–0.88)
0	≥1	67	0	0.00 (0.00–1.79)	145	2	0.31 (0.04–1.10)	122	4	0.78 (0.21–1.99)	220	0	0.00 (0.00–0.42)
1	0	52	0	0.00 (0.00–2.16)	110	1	0.18 (0.00–1.03)	37	5	2.90 (0.94–6.77)	104	0	0.00 (0.00–1.00)
1	≥1	82	1	0.35 (0.01–1.97)	234	5	0.50 (0.16–1.17)	209	5	0.55 (0.18–1.29)	600	0	0.00 (0.00–0.16)

Abbreviations: ABCD, Age ≥ 60 years, BNP level ≥ 300 pg/mL or NT-proBNP level ≥ 300 pg/mL, Creatinine clearance <50 mL/min, Dimension of the left atrium ≥45 mm; ATT, antithrombotic therapy; BNP, B-type natriuretic peptide; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 (2 points), Diabetes mellitus, prior Stroke or transient ischemic attack (2 points), Vascular disease, Age 65–74 years, female gender category; CI, confidence interval; ICH, intracranial hemorrhage; NOAC, non-vitamin K antagonist oral anticoagulant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAPT, single anti-platelet; VKA, vitamin K antagonist.

0.14 events/100 P-Y, 95% CI 0.04–0.35; VKA 0.27 events/100 P-Y, 95% CI 0.09–0.62; NOAC, 0.05 events/100 P-Y, 95% CI 0.01–0.18). This trend was consistent with either ABCD score or non-gender CHA_2DS_2-VASc score classification (Table 3).

Figures 2 and 3 illustrate the Kaplan–Meier analysis of composite TEs and major bleeding events after applying ABCD and non-gender CHA_2DS_2-VASc scores for patient risk stratification. In patients with low composite thrombotic risk, there was no difference in the occurrence of composite TEs following ATT. There was a significantly higher incidence of composite TEs following ATT in high composite thrombotic risk patients with a non-gender CHA_2DS_2-VASc score of 1 and ABCD score ≥1 (Log-rank test, p = .002) (Figure 2). With respect to major bleeding events, ATT in high-risk patients with a non-gender CHA_2DS_2-VASc score of 1 and ABCD score ≥1 showed a significant difference in the occurrence of major bleeding events according to treatment (log-rank test, p = .002) (Figure 3).

Figures 4 and 5 show the NCB analysis for the entire follow-up period. The patients without ATT were compared with the group that received ATT, and comparisons among ATT regimens were conducted by applying different risk weight values. When no ATT was compared with SAPT, the NCB was neutral across all four risk groups (Figure 4). When no ATT was compared with VKA, the NCB showed a tendency to favor no ATT. When no ATT was compared with NOAC, for all NCB models, patients with a non-gender CHA_2DS_2-VASc score of 1 and ABCD score ≥1 tended to show positive NCBs and generally favored NOAC (weight by Eikelboom et al., NCB = 1.44, 95% CI -0.17–7.10; by Lip et al., NCB = 1.53, 95% CI -0.10–7.21; by Connolly et al., NCB = 1.48, 95% CI −0.16 to 7.16). In comparisons

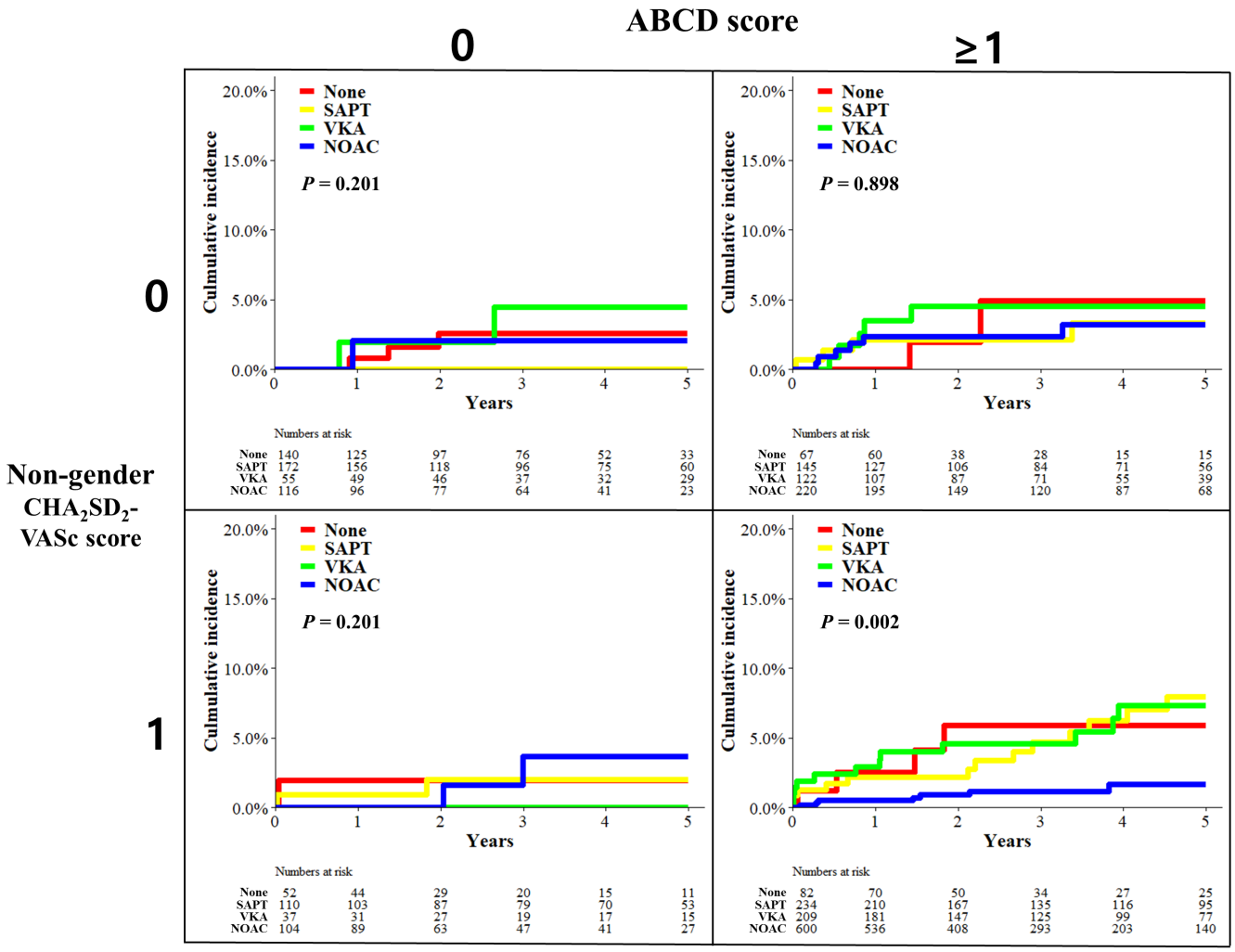

FIGURE 2 Kaplan–Meier curves for composite thrombotic events according to antithrombotic treatment stratified by the ABCD and non-gender CHA_2DS_2-VASc scores. Composite thrombotic events were defined as ischemic stroke, systemic embolism, and myocardial infarction. ABCD indicates Age ≥ 60 years, BNP level ≥ 300 pg/mL or NT-proBNP level ≥ 300 pg/mL, Creatinine clearance <50 mL/min, Dimension of the left atrium ≥45 mm; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, prior Stroke or transient ischemic attack (2 points), Vascular disease, Age 65–74 years, female gender category; ATT, antithrombotic therapy; SAPT, single anti-platelet; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

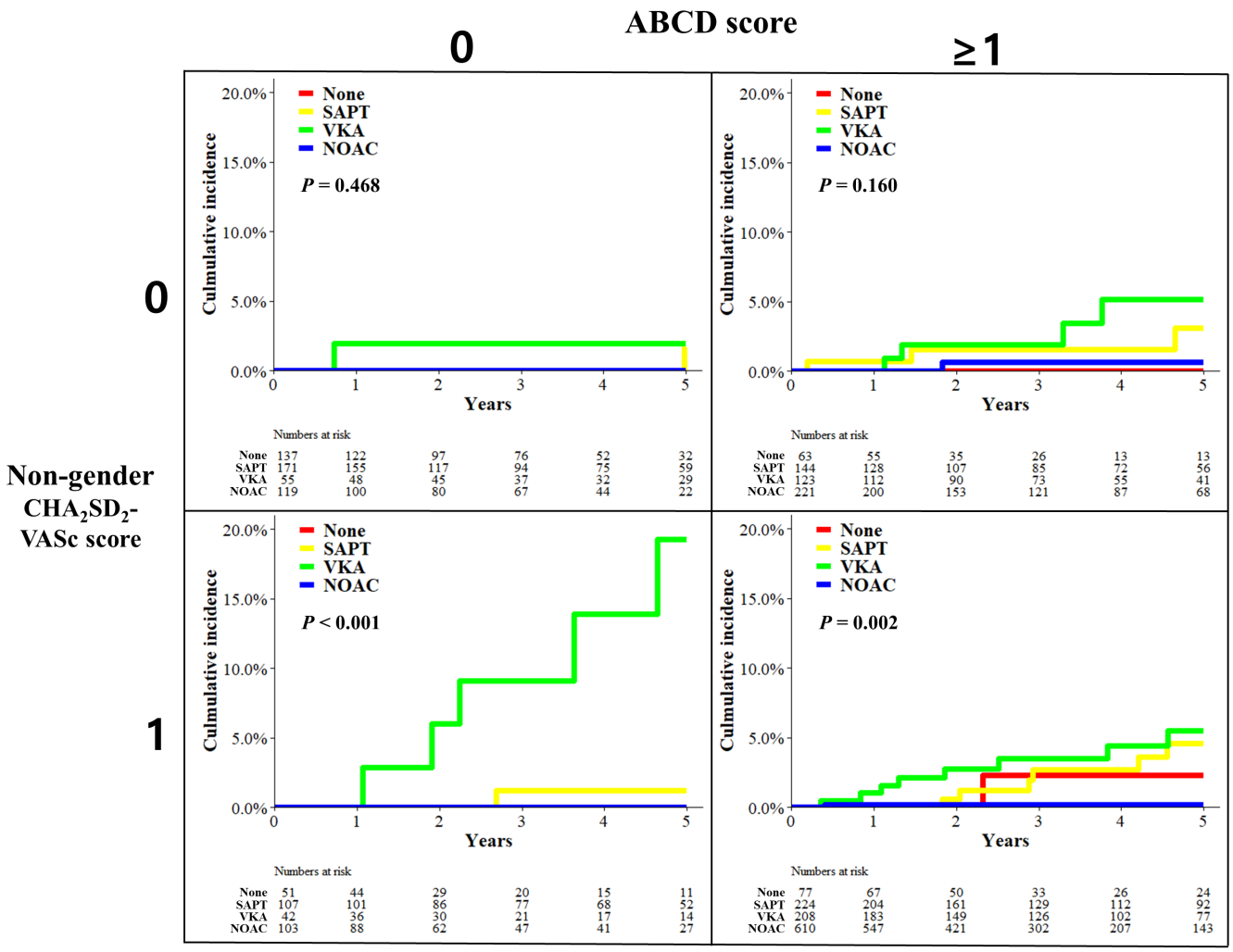

FIGURE 3 Kaplan–Meier curves for total major bleeding events according to antithrombotic treatment stratified by the ABCD and non-gender CHA_2DS_2-VASc scores. ABCD indicates Age ≥ 60 years, BNP level ≥ 300 pg/mL or NT-proBNP level ≥ 300 pg/mL, Creatinine clearance <50 mL/min, Dimension of the left atrium ≥45 mm; ATT, antithrombotic therapy; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, prior Stroke or transient ischemic attack (2 points), Vascular disease, Age 65–74 years, female gender category; SAPT, single anti-platelet; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

among the three ATTs (SAPT, VKA, NOAC), the comparison between SAPT and VKA failed to show differences across all risk groups, and the NCB of NOAC was significantly superior to the other ATTs (VKA and SAPT) in patients with a non-gender CHA_2DS_2-VASc score of 1 and ABCD score ≥1 (Figure 5).

4 | DISCUSSION

Our main findings in this real-world data analysis are as follows (1): Regardless of ATT, similar incidences of TEs were observed in patients classified as low to intermediate risk by a non-gender CHA_2DS_2-VASc score of 0–1, but 86.2% of them were treated with ATTs at the physicians' discretion (Figure S1) and (2) although the NCB of SAPT and VKA failed to compare with no ATT in patients with low to intermediate risk, NOAC showed a statistically significant NCB in comparison with other ATTs in patients with a non-gender CHA_2DS_2-VASc score of 1 and ABCD score ≥1.

These findings represent a clinically unmet need for stroke prevention in low- to intermediate-risk patients, and our proposed detailed risk stratification scheme for these patients determined NOAC as a favorable ATT regimen with positive NCBs.

According to the current guidelines, patients with a non-gender CHA_2DS_2-VASc score of 1 are classified as low to intermediate stroke risk patients, and ATT should be considered and individualized according to physicians' discretion, NCBs, and preferences.[7] In this regard, the ABCD score reflecting biomarkers contributing to thrombogenicity, and the degree of anatomical remodeling was proposed for detailed stroke risk stratification of Asian AF patients within a gray zone.[12] The results of this study reinforce that the ABCD score may help in identifying truly low-risk patients who do not need ATT among the low to intermediate-risk AF patients.

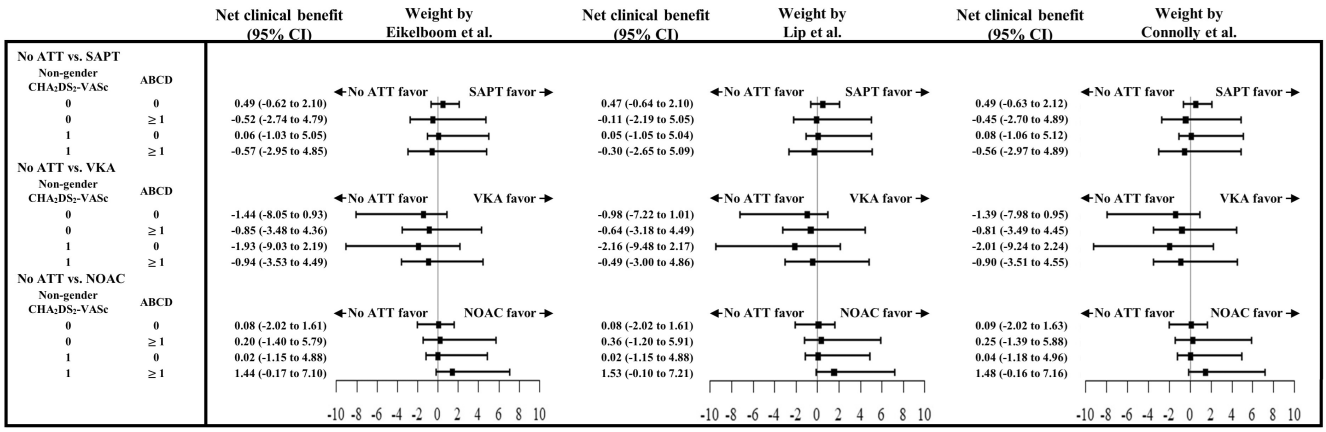

FIGURE 4 Net clinical benefit analyses for no antithrombotic treatment in comparison with three antithrombotic treatments according to the ABCD score, non-gender CHA_2DS_2-VASc score, and three weight models of net clinical benefit. NCB indicates net clinical benefit; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, prior Stroke or transient ischemic attack (2 points), Vascular disease, Age 65–74 years, female gender category; ABCD, Age ≥ 60 years, BNP level ≥ 300 pg/mL or NT-proBNP level ≥ 300 pg/mL, Creatinine clearance <50 mL/min, Dimension of the left atrium ≥45 mm; ATT, antithrombotic therapy; SAPT, single anti-platelet; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

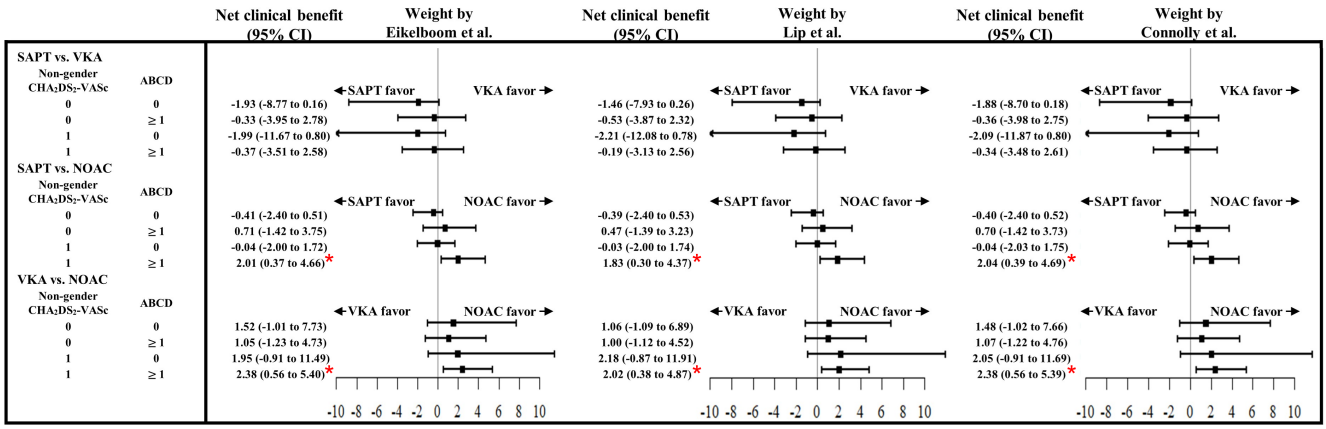

FIGURE 5 Net clinical benefit analyses between antithrombotic treatments according to the ABCD score, non-gender CHA_2DS_2-VASc score, and three weight models of net clinical benefit. *Net clinical benefit analyses with significant differences. NCB indicates net clinical benefit; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, prior Stroke or transient ischemic attack (2 points), Vascular disease, Age 65–74 years, female gender category; ABCD, Age ≥ 60 years, BNP level ≥ 300 pg/mL or NT-proBNP level ≥ 300 pg/mL, Creatinine clearance <50 mL/min, Dimension of the left atrium ≥45 mm; ATT, antithrombotic therapy; SAPT, single anti-platelet; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

In other studies of low- to intermediate-risk patients, age 60–64 years (HR 1.20, 95% CI 1.13–1.27),[26] elevated NT-proBNP (HR 2.35, 95% CI 1.62–3.40),[27] elevated creatinine clearance (HR 1.09, 95% CI 1.13–1.04),[28] and enlarged LA size[29] all contribute to future stroke risk. The ABCD score more clearly stratifies patients in addition to the non-gender CHA_2DS_2-VASc score, which consists only of clinical risk factors, and can help identify patients with a truly low stroke risk where no ATT is needed.

According to the real-world data in this study, approximately 86% of patients were treated with ATTs according to the physicians' discretions and their preferences. Thus, physicians are concerned about the residual stroke risk in each patient overlooked by the CHA_2DS_2-VASc score. By applying the ABCD score to the low- to intermediate-risk group, patients who potentially benefit from ATT with a positive NCB could be identified. Meanwhile, it is also possible to avoid unnecessary ATT for truly low-risk patients.

Given the improved efficacy and safety of NOAC compared to VKA, our NCB analyses regarding the mortality of our patients suggest that the use of NOAC could potentially improve mortality. Previous studies have shown that the NCB associated with NOAC is generally positive for patients with one additional stroke risk factor when balancing ischemic stroke reduction for severe bleeding.[30] In the realm of treating patients, treatment for AF patients tends to prioritize stroke prevention over treatment-induced bleeding risk.[31]

The NCB is an index that judges the appropriateness of benefits and risks in treating AF patients. This concept was first introduced

by Singer et al., and at that time, only the relationship between ischemic stroke and ICH was identified.[12] However, this analysis did not include MI and other major bleeding events, which are major events that may occur during ATT, and more recent studies included major bleeding events other than ICH.[13–15] According to our data, the incidence of MI and major bleeding events other than ICH occurred at sufficiently high rates to be non-negligible. Therefore, this study derived a more realistic NCB by applying a weight including major bleeding events and MI to the NCB.

A limitation of this retrospective analysis study was that the number of events that occurred in the patients was small. In some cases, data on BNP levels, creatinine clearance, or LA size were not completely available. However, this did not diminish the ability of the ABCD score to subdivide risk among AF patients with low to intermediate risk. Because the risk factors of AF patients are not fixed and have dynamic characteristics over time, future research is needed to determine the incidence rate according to changes in ABCD and CHA_2DS_2-VASc scores over time. Regarding the use of VKA, the optimal international normalized ratio (INR) index was 2–3. However, multiple INRs could not be obtained at baseline due to the limitations of the retrospective nature of this study. In addition, since this study was conducted only on Korean patients, additional research is needed for application to other ethnic groups.

5 | CONCLUSIONS

In this Korean AF cohort at low to intermediate stroke risk, NOAC showed significant NCB advantages over the other ATTs (VKA and SAPT) in AF patients with an ABCD score ≥1. With further risk stratification by the ABCD score, the potential NCB of NOAC may be expected in Korean AF patients with low to intermediate stroke risk.

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CONFLICT OF INTEREST STATEMENT

None.

DECLARATIONS

Approval of the research protocol: This study was approved by the institutional review board of each institution.

Informed consent: Written informed consent was waived due to the retrospective cohort study design.

Registry and the Registration No. of the study/trial: IRB No. 2005–018-19317.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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