

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)

Moonki Jung MD¹ | Kyeongmin Byeon MD¹ | Ki-Woon Kang MD² | Wang-Soo Lee MD² | Sang Wook Kim MD² | Yae Min Park MD³ | You Mi Hwang MD⁴ | Sung Ho Lee MD⁵ | Eun-Sun Jin MD⁶ | Seung-Young Roh MD⁷  | Jin Seok Kim MD⁷ | Jinhee Ahn MD⁸  | So-Ryoung Lee MD⁹ | Eue-Keun Choi MD⁹ | Min-Soo Ahn MD¹⁰ | Eun Mi Lee MD¹¹ | Hwan-Cheol Park MD¹² | Ki Hong Lee MD¹³ | Min Kim MD¹⁴ | Joon Hyouk Choi MD¹⁵ | Jum Suk Ko MD¹⁶ | Jin Bae Kim MD¹⁷ | Changsoo Kim MD¹⁸ | Gregory Y. H. Lip MD^{19,20}  | Seung Yong Shin MD²  | the Clinical Survey on Stroke Prevention in patients with Atrial Fibrillation (CS-SPAF) Investigators

¹Department of Cardiology, Heart and Brain Hospital, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong-si, Republic of Korea

²Cardiovascular & Arrhythmia Center, Chung-Ang University Hospital, Chung-Ang University, Seoul, Republic of Korea

³Division of Cardiology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea

⁴Division of Cardiology, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Republic of Korea

⁵Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

⁶Cardiovascular Center, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea

⁷Division of Cardiology, Department of Internal Medicine, Korea University College of Medicine and Korea University Medical Center, Seoul, Republic of Korea

⁸Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea

⁹Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

¹⁰Division of Cardiology, Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University, Wonju College of Medicine, Wonju, Republic of Korea

¹¹Division of Cardiology, Department of Internal Medicine, Wonkwang University Sanbon Hospital, Gunpo, Republic of Korea

¹²Department of Cardiology, Hanyang University Guri Hospital, Guri City, Republic of Korea

¹³Division of Cardiology, Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea

¹⁴Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Republic of Korea

¹⁵Division of Cardiology, Department of Internal Medicine, School of Medicine, Jeju National University, Jeju National University Hospital, Jeju, Republic of Korea

¹⁶Department of Cardiovascular Medicine, Regional Cardiocerebrovascular Center, Wonkwang University Hospital, Iksan, Republic of Korea

¹⁷Division of Cardiology, Department of Internal Medicine, Kyung Hee University Hospital, School of Medicine, Kyung Hee University, Seoul, Republic of Korea

¹⁸Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

¹⁹Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK

²⁰Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark

Moonki Jung and Kyeongmin Byeon equally contributed to this work.

Gregory Y. H. Lip and Seung Yong Shin are joint senior authors of this work.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. *Journal of Arrhythmia* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Heart Rhythm Society.

Correspondence

Seung Yong Shin, Cardiovascular & Arrhythmia Center, Chung-Ang University Hospital, Chung-Ang University, 102, Heukseok-ro, Dongjak-gu, Seoul 06973, Republic of Korea.
Email: theshin04@cau.ac.kr

Funding information

Korea Disease Control and Prevention Agency, Grant/Award Number: 2020ER630100

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 CHA₂DS₂-VASc scores 0–1. A net clinical benefit (NCB) analysis of ATT may guide stroke prevention strategies in AF with non-gender CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-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 populations¹ 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 (CHA₂DS₂-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 CHA₂DS₂-VASc score of 0).^{6–8} For AF patients with a 'low to intermediate risk' of stroke with a non-gender CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-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:

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

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:

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

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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ score of 0 and 1428 (57.9%) had a non-gender $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ score of 1 and ABCD score ≥ 1 showed a higher incidence of composite TEs compared to the lower risk group with a non-gender $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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

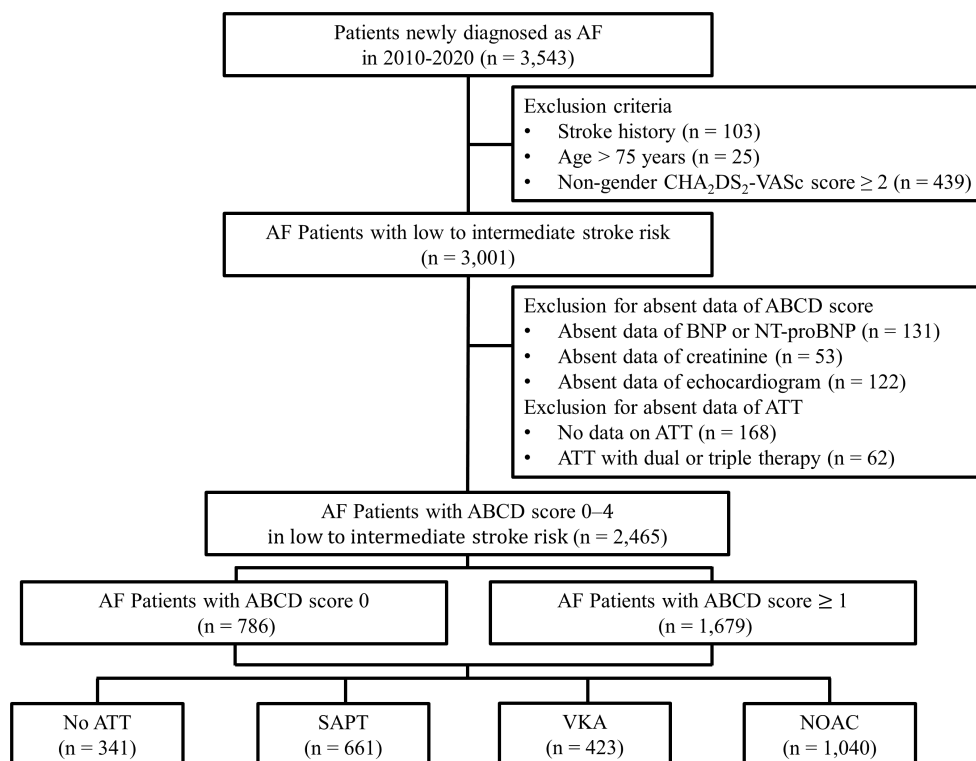


FIGURE 1 Flowchart of the study population for calculating net clinical benefit amongst atrial fibrillation patients with non-gender $\text{CHA}_2\text{DS}_2\text{-VASc}$ scores 0–1 after incident atrial fibrillation. AF indicates atrial fibrillation; $\text{CHA}_2\text{DS}_2\text{-VASc}$, congestive 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.

	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 ₂ DS 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

TABLE 1 Baseline Characteristics in Atrial Fibrillation Patients with Non-gender CHA₂DS₂-VASc scores 0–1.

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; CHA₂DS₂-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 CHA₂DS₂-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 ₂ DS 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 ₂ DS 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 ₂ DS 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; CHA₂DS₂-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 CHA₂DS₂-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 ₂ DS ₂ - VAsC 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 ₂ DS ₂ - VAsC 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 ₂ DS ₂ - VAsC 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; CHA₂DS₂-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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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

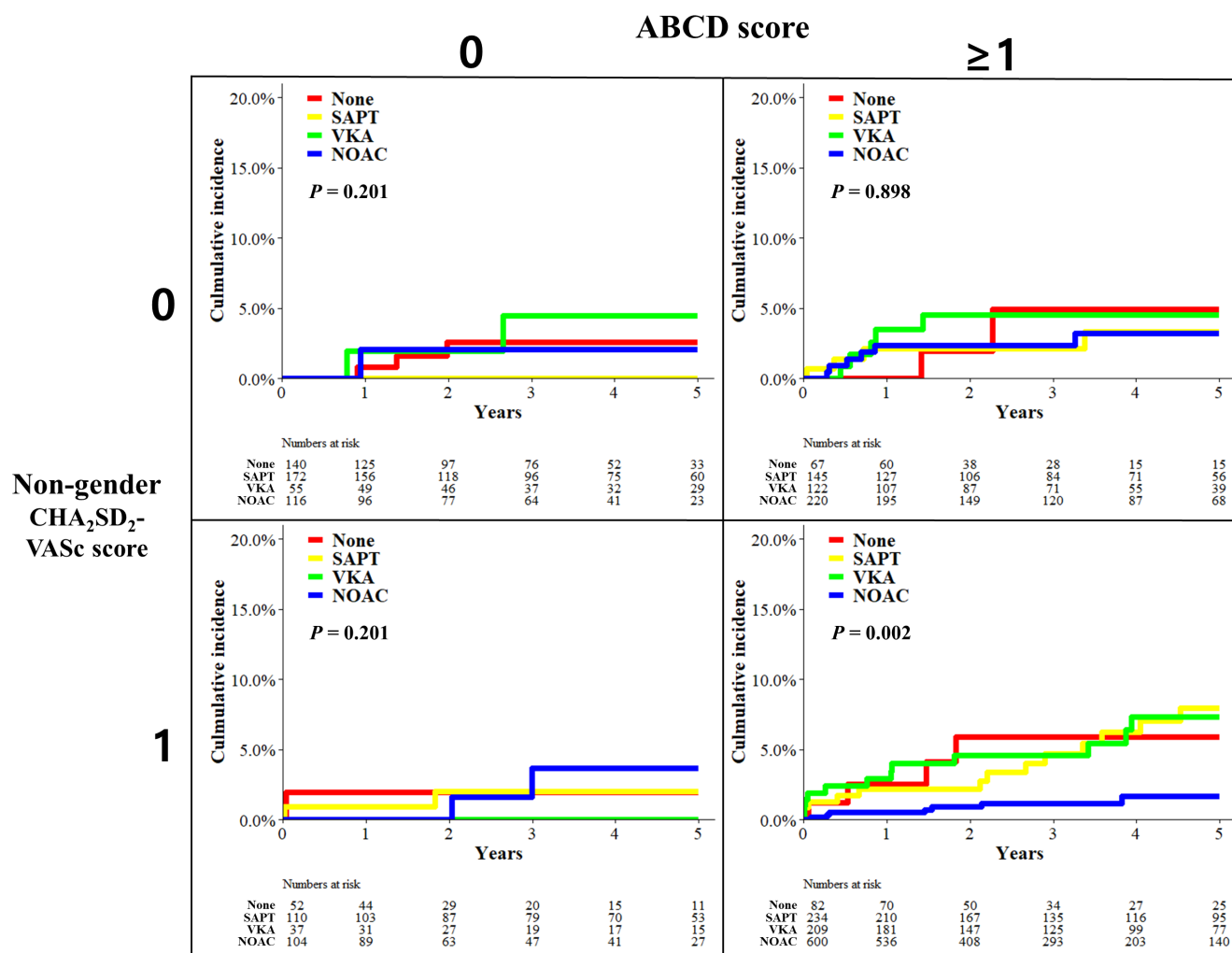


FIGURE 2 Kaplan–Meier curves for composite thrombotic events according to antithrombotic treatment stratified by the ABCD and non-gender $\text{CHA}_2\text{DS}_2\text{-VASc}$ scores. Composite thrombotic events were defined as ischemic stroke, systemic embolism, and myocardial infarction. ABCD indicates Age ≥ 60 years, BNP level $\geq 300\text{pg/mL}$ or NT-proBNP level $\geq 300\text{pg/mL}$, Creatinine clearance $<50\text{mL/min}$, Dimension of the left atrium $\geq 45\text{mm}$; $\text{CHA}_2\text{DS}_2\text{-VASc}$, 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.

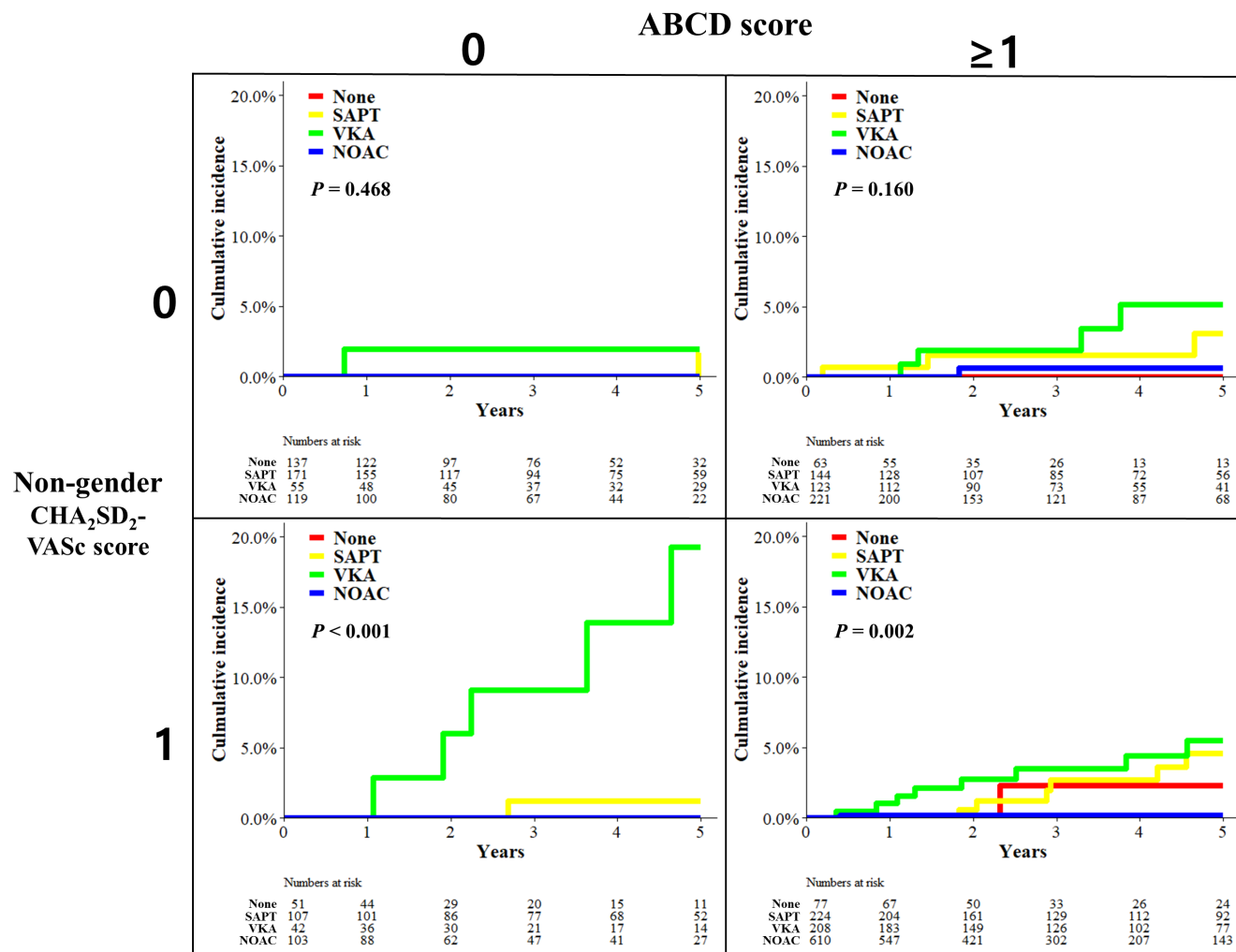


FIGURE 3 Kaplan–Meier curves for total major bleeding events according to antithrombotic treatment stratified by the ABCD and non-gender CHA₂DS₂-VASc scores. ABCD indicates Age ≥ 60 years, BNP level ≥ 300 pg/mL or NT-proBNP level ≥ 300 pg/mL, Creatinine clearance < 50 mL/min, Dimension of the left atrium ≥ 45 mm; ATT, antithrombotic therapy; CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-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.

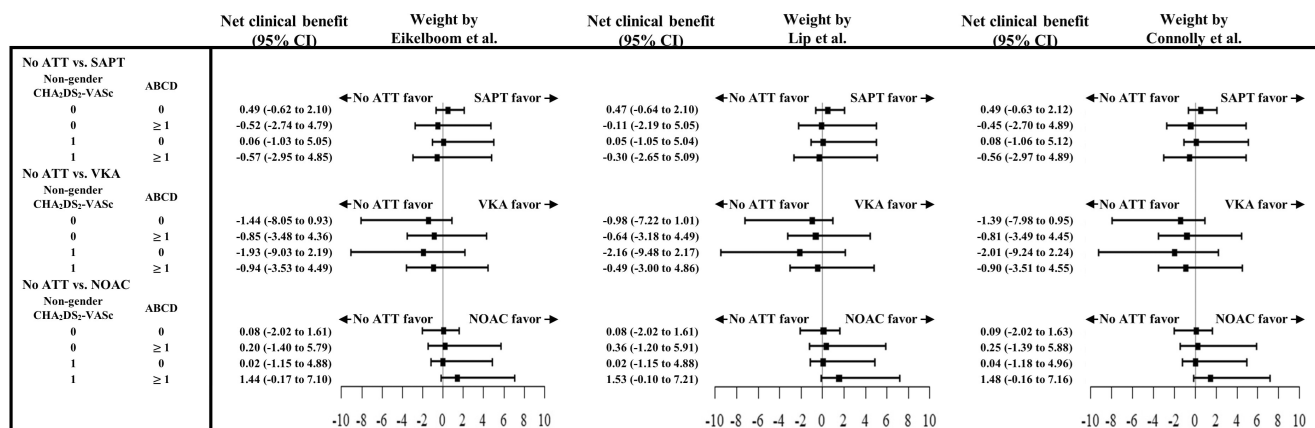


FIGURE 4 Net clinical benefit analyses for no antithrombotic treatment in comparison with three antithrombotic treatments according to the ABCD score, non-gender $\text{CHA}_2\text{DS}_2\text{-VASc}$ score, and three weight models of net clinical benefit. NCB indicates net clinical benefit; $\text{CHA}_2\text{DS}_2\text{-VASc}$, 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.

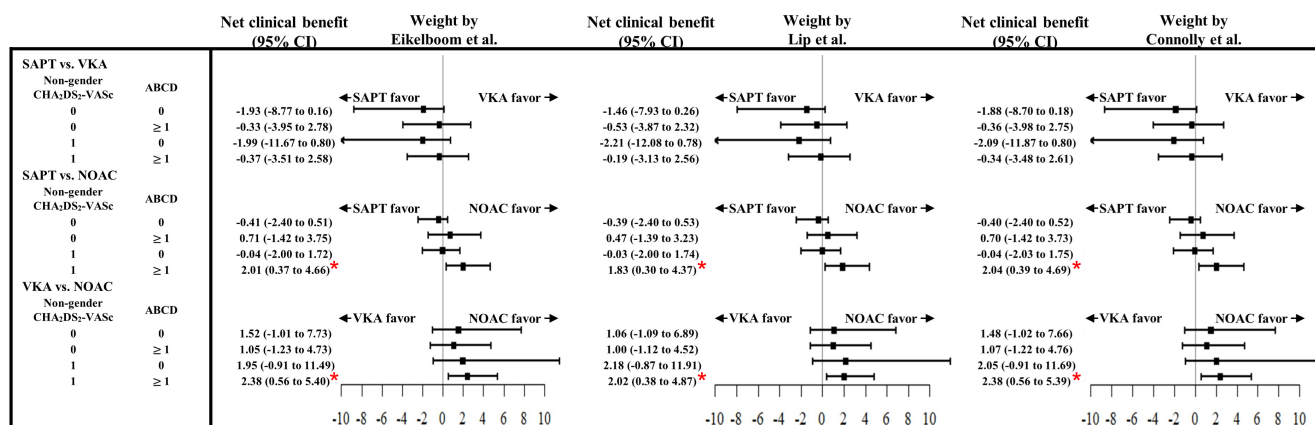


FIGURE 5 Net clinical benefit analyses between antithrombotic treatments according to the ABCD score, non-gender $\text{CHA}_2\text{DS}_2\text{-VASc}$ score, and three weight models of net clinical benefit. *Net clinical benefit analyses with significant differences. NCB indicates net clinical benefit; $\text{CHA}_2\text{DS}_2\text{-VASc}$, 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 size²⁹ all contribute to future stroke risk. The ABCD score more clearly stratifies patients in addition to the non-gender $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 $\text{CHA}_2\text{DS}_2\text{-VASc}$ 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 CHA₂DS₂-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.

ACKNOWLEDGMENTS

We would like to thank Song Yi Son and Hyejin Ryu for the study coordination.

FUNDING INFORMATION

This study was funded by the Division of Cardiovascular Disease in Korea Disease Control and Prevention Agency (2020ER630100).

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.

ORCID

Seung-Young Roh  <https://orcid.org/0000-0002-0854-9079>

Jinhee Ahn  <https://orcid.org/0000-0001-6179-1254>

Gregory Y. H. Lip  <https://orcid.org/0000-0002-7566-1626>

Seung Yong Shin  <https://orcid.org/0000-0002-3408-6899>

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22(8):983–8.
2. Bassand J-P, Virdone S, Badoz M, Verheugt FWA, Camm AJ, Cools F, et al. Bleeding and related mortality with NOACs and VKAs in newly diagnosed atrial fibrillation: results from the GARFIELD-AF registry. *Blood Adv*. 2021;5(4):1081–91.
3. Burdett P, Lip GYH. Atrial fibrillation in the UK: predicting costs of an emerging epidemic recognizing and forecasting the cost drivers of atrial fibrillation-related costs. *Eur Heart J*. 2022;8(2):187–94.
4. Lip GYH, Nieuwlaet R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263–72.
5. Pisters R, Lane DA, Marin F, Camm AJ, Lip GYH. Stroke and thromboembolism in atrial fibrillation—systematic review of stroke risk factors and risk stratification schema. *Circ J* 2012;CJ-12, 76, 2289–2304.
6. Chao T-F, Joung B, Takahashi Y, Lim TW, Choi E-K, Chan Y-H, et al. 2021 focused update consensus guidelines of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation: executive summary. *Thromb Haemost*. 2022;122(1):20–47.
7. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373–498.
8. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74(1):104–32.
9. Shin SY, Han SJ, Kim JS, Im SI, Shim J, Ahn J, et al. Identification of markers associated with development of stroke in “Clinically Low-Risk” atrial fibrillation patients. *J Am Heart Assoc*. 2019;8(21):e012697.
10. Friberg L, Rosenqvist M, Lip GYH. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation*. 2012;125(19):2298–307.
11. Pisters R, Nieuwlaet R, Lane DA, Crijns HJGM, Lip GYH. Potential net clinical benefit of population-wide implementation of apixaban and dabigatran among European patients with atrial fibrillation. *Thromb Haemost*. 2013;109(2):328–36.
12. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med*. 2009;151(5):297–305.
13. Connolly SJ, Eikelboom JW, Ng J, Hirsh J, Yusuf S, Pogue J, et al. Net clinical benefit of adding clopidogrel to aspirin therapy in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable. *Ann Intern Med*. 2011;155(9):579–86.

14. Eikelboom JW, Connolly SJ, Hart RG, Wallentin L, Reilly P, Oldgren J, et al. Balancing the benefits and risks of 2 doses of dabigatran compared with warfarin in atrial fibrillation. *J Am Coll Cardiol*. 2013;62(10):900–8.
15. Lip GYH, Skjøth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. *Thromb Haemost*. 2015;114(10):826–34.
16. Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? *Circulation*. 2018;137(8):832–40.
17. Cockcroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
18. Lang RM, Badano LP, Mor-Avi V, Afzalalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imag*. 2015;16(3):233–71.
19. Jung M, Byeon K, Kang K-W, Park YM, Hwang YM, Lee SH, et al. Validation of biomarker-based ABCD score in atrial fibrillation patients with a non-gender CHA2DS2-VASc score 0–1: a Korean multi-center cohort. *Yonsei Med J*. 2022;63:892–901.
20. Charitos EI, Stierle U, Ziegler PD, Baldewig M, Robinson DR, Sievers H-H, et al. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. *Circulation*. 2012;126(7):806–14.
21. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke*. 1993;24(1):35–41.
22. Schulman S, Kearon C, the SOCOAOTS. Standardization committee of the international society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692–4.
23. Active SC. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. *Am Heart J*. 2006;151(6):1187–93.
24. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J*. 2009;157(5):805–10.
25. Krishnamoorthy K, Lee M. New approximate confidence intervals for the difference between two Poisson means and comparison. *J Stat Comput Simul*. 2013;83(12):2232–43.
26. Kim T-H, Yang P-S, Yu HT, Jang E, Uhm J-S, Kim J-Y, et al. Age threshold for ischemic stroke risk in atrial fibrillation: cohort data covering the entire Korean population. *Stroke*. 2018;49(8):1872–9.
27. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Christersson C, Ezekowitz J, et al. N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE trial (Apixaban for the prevention of stroke in subjects with atrial fibrillation). *J Am Coll Cardiol*. 2013;61(22):2274–84.
28. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R2CHADS2 index in the ROCKET AF (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) and ATRIA (AnTicoagulation and risk factors In atrial fibrillation) study cohorts. *Circulation*. 2013;127(2):224–32.
29. Vinereanu D, Lopes RD, Mulder H, Gersh BJ, Hanna M, de Barros E, et al. Echocardiographic risk factors for stroke and outcomes in patients with atrial fibrillation anticoagulated with apixaban or warfarin. *Stroke*. 2017;48(12):3266–73.
30. Banerjee A, Lane DA, Torp-Pedersen C, Lip GYH. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world'atrial fibrillation population: a modelling analysis based on a nationwide cohort study. *Thromb Haemost*. 2012;107(3):584–9.
31. Lane DA, Lip GYH. Patient's values and preferences for stroke prevention in atrial fibrillation: balancing stroke and bleeding risk with oral anticoagulation. *Thromb Haemost*. 2014;112(3):381–3.

SUPPORTING INFORMATION

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

How to cite this article: Jung M, Byeon K, Kang K-W, Lee W-S, Kim SW, Park YM, et al. the Clinical Survey on Stroke Prevention in patients with Atrial Fibrillation (CS-SPAF) Investigators. 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). *J Arrhythmia*. 2023;39:376–387. <https://doi.org/10.1002/joa3.12840>