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*A Korean Multi-Center Cohort*

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# Validation of Biomarker-Based ABCD Score in Atrial Fibrillation Patients with a Non-Gender $CHA_2DS_2$-VASc Score 0–1: A Korean Multi-Center Cohort

Moonki Jung[1*], Kyeongmin Byeon[1*], Ki-Woon Kang[2], Yae Min Park[3], You Mi Hwang[4], Sung Ho Lee[5], Eun-Sun Jin[6], Seung-Young Roh[7], Jin Seok Kim[7], Jinhee Ahn[8], So-Ryoung Lee[9], Eue-Keun Choi[9], Min-soo Ahn[10], Eun Mi Lee[11], Hwan-Cheol Park[12], Ki Hong Lee[13], Min Kim[14], Joon Hyouk Choi[15], Jum Suk Ko[16], Jin Bae Kim[17], Changsoo Kim[18], Gregory Y.H. Lip[19,20], Seung Yong Shin[2], and Clinical Survey on Stroke Prevention in Patients with Atrial Fibrillation (CS-SPAF) Investigators

[1]Department of Cardiology, Heart and Brain Hospital, Chung-Ang University Gwangmyeong Hospital, College of Medicine, Chung-Ang University, Gwangmyeong;
[2]Cardiovascular & Arrhythmia Center, Chung-Ang University Hospital, College of Medicine, Chung-Ang University, Seoul;
[3]Division of Cardiology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon;
[4]Division of Cardiology, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon;
[5]Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul;
[6]Cardiovascular Center, Kyung Hee University Hospital at Gangdong, Seoul;
[7]Division of Cardiology, Department of Internal Medicine, Korea University College of Medicine and Korea University Medical Center, Seoul;
[8]Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, Busan;
[9]Department of Internal Medicine, Seoul National University Hospital, Seoul;
[10]Division of Cardiology, Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University, Wonju College of Medicine, Wonju;
[11]Division of Cardiology, Department of Internal Medicine, Wonkwang University Sanbon Hospital, Gunpo;
[12]Department of Cardiology, Hanyang University Guri Hospital, Guri;
[13]Division of Cardiology, Department of Internal Medicine, Chonnam National University Medical School, Gwangju;
[14]Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju;
[15]Division of Cardiology, Department of Internal Medicine, School of Medicine, Jeju National University, Jeju National University Hospital, Jeju;
[16]Department of Cardiovascular Medicine, Regional Cardiocerebrovascular Center, Wonkwang University Hospital, Iksan;
[17]Division of Cardiology, Department of Internal Medicine, Kyung Hee University Hospital, School of Medicine, Kyung Hee University, Seoul;
[18]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Korea;
[19]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom;
[20]Department of Clinical Medicine, Aalborg University, Denmark.

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**Co-corresponding authors:** Gregory Y.H. Lip, MD, Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Foundation Building, Brownlow Hill, Liverpool, L69 7TX, United Kingdom.
E-mail: Gregory.Lip@liverpool.ac.uk and
Seung Yong Shin, MD, Cardiovascular & Arrhythmia Center, Chung-Ang University Hospital, College of Medicine, Chung-Ang University, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Korea.
E-mail: theshin04@cau.ac.kr

*Moonki Jung and Kyeongmin Byeon contributed equally to this work.
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**Purpose:** Atrial fibrillation (AF) patients with low to intermediate risk, defined as non-gender $CHA_2DS_2$-VASc score of 0–1, are still at risk of stroke. This study verified the usefulness of ABCD score [age (≥60 years), B-type natriuretic peptide (BNP) or N-terminal pro-BNP (≥300 pg/mL), creatinine clearance (<50 mL/min/1.73 $m^2$), and dimension of the left atrium (≥45 mm)] for stroke risk stratification in non-gender $CHA_2DS_2$-VASc score 0–1.

**Materials and Methods:** This multi-center cohort study retrospectively analyzed AF patients with non-gender $CHA_2DS_2$-VASc score 0–1. The primary endpoint was the incidence of stroke with or without antithrombotic therapy (ATT). An ABCD score was validated.

**Results:** Overall, 2694 patients [56.3±9.5 years; female, 726 (26.9%)] were followed-up for 4.0±2.8 years. The overall stroke rate was 0.84/100 person-years (P-Y), stratified as follows: 0.46/100 P-Y for an ABCD score of 0; 1.02/100 P-Y for an ABCD score ≥1. The ABCD score was superior to non-gender $CHA_2DS_2$-VASc score in the stroke risk stratification (C-index=0.618, $p$=0.015; net reclassification improvement=0.576, $p$=0.040; integrated differential improvement=0.033, $p$=0.066). ATT was prescribed in 2353 patients (86.5%), and the stroke rate was significantly lower in patients receiving non-vitamin K antagonist oral anticoagulant (NOAC) therapy and an ABCD score ≥1 than in those without ATT (0.44/100 P-Y vs. 1.55/100 P-Y; hazard ratio=0.26, 95% confidence interval 0.11–0.63, $p$=0.003).

**Conclusion:** The biomarker-based ABCD score demonstrated improved stroke risk stratification in AF patients with non-gender $CHA_2DS_2$-VASc score 0–1. Furthermore, NOAC with an ABCD score ≥1 was associated with significantly lower stroke rate in AF patients with non-gender $CHA_2DS_2$-VASc score 0–1.

**Key Words:** Atrial fibrillation, risk stratification, stroke, ABCD score

## INTRODUCTION

Atrial fibrillation (AF) is an independent risk factor that increases the risk of stroke and thromboembolism (TE) more than five-fold,[1] accounting for 10%–15% of all strokes,[2] and is associated with substantial mortality, morbidity,[3] and healthcare costs.[4] Many studies have focused on how best to determine the group of patients who should receive antithrombotic therapy (ATT) to minimize the risk of stroke that accompanies the diagnosis of AF. The latest guidelines stratify the stroke risk of individual patients with AF using the $CHA_2DS_2$-VASc score [congestive heart failure, hypertension (HTN), age ≥75 years (2 points), diabetes mellitus (DM), previous stroke event or transient ischemic attack (2 points), vascular disease, age 65–74 years, and female sex].[5-8]

For more detailed risk stratification in patients with AF at low to intermediate risk, a biomarker-based ABCD score [age ≥60 years, B-type natriuretic peptide (BNP) level or N-terminal pro-BNP (NT-proBNP) level ≥300 pg/mL, creatinine clearance <50 mL/min/1.73 $m^2$, dimension of the left atrium (LA) ≥45 mm] was proposed.[9] As the ABCD score includes biomarkers associated with the development of stroke,[10-14] it may be superior to the $CHA_2DS_2$-VASc score in identifying patients who truly have a low stroke risk and in selecting patients who potentially benefit from ATT. Therefore, the primary goal of this study was to verify the usefulness of the ABCD score for stroke risk stratification in patients with a non-gender $CHA_2DS_2$-VASc score 0–1. The secondary goal was to investigate the effectiveness of ATT in this low to intermediate risk patient group which was stratified by the ABCD score.

## MATERIALS AND METHODS

### Study design and population

This study had a multi-center retrospective cohort design. Between January 1, 2010, and December 31, 2019, we retrospectively reviewed the medical records of patients who were diagnosed and treated for non-valvular AF at 13 domestic institutions in Korea. Among patients who had no previous stroke or TE at the time of enrollment, patients with a non-gender $CHA_2DS_2$-VASc score 0–1 and adults aged 18 years or older were enrolled. Patients receiving anti-coagulant therapy for causes other than AF, such as the presence of mechanical valves, pulmonary embolism, or deep vein thrombosis, were excluded, as were patients with moderate to severe mitral stenosis or mitral mechanical valve replacement.

The non-gender $CHA_2DS_2$-VASc score was calculated as follows: 2 points for age ≥75 years and stroke or transient ischemic attack and 1 point for congestive heart failure [or left ventricular ejection fraction (LVEF) ≤40%], HTN, age 65–74 years, DM, and vascular disease (previous myocardial infarction, peripheral arterial disease, or aortic plaque).[15,16] The ABCD score was calculated as follows: 1 point for age ≥60 years, BNP level or NT-proBNP level ≥300 pg/mL, creatinine clearance <50 mL/min/1.73 $m^2$, and dimension of the LA ≥45 mm (range, 0–4 points).[9,17,18] Since this was a retrospective study, there were some cases in which data for the BNP level, creatinine clearance, or dimension of the LA were not obtained completely. In those cases, patients whose ABCD score was not classified as 0, 1, or higher were excluded from the study.

### Data collection

The medical records of all patients were analyzed and included the demographic data, cardiovascular risk factors, transthoracic echocardiography findings, and blood test results (BNP, NT-proBNP, and creatinine levels). Creatinine clearance was calculated using the Cockcroft-Gault formula[19]; LVEF was calculated using Simpson's biplane method, and dimensions of the LA were measured in M-mode of the parasternal long axis view of transthoracic echocardiography.[20] According to the ATT prescribed after the diagnosis of AF, patients were classified and reviewed as groups of no ATT, single anti-platelet (SAPT) therapy using aspirin or a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor), non-vitamin K antagonist oral anticoagulant (NOAC) therapy (apixaban, dabigatran, rivaroxaban, or edoxaban), vitamin K antagonist (VKA) therapy, and dual antiplatelet therapy using both aspirin and a P2Y12 inhibitor. Data was censored at the events of death, change of ATT, and end of study observation.

### Diagnosis of AF, cardio-embolic stroke/TE, and hemorrhagic events

The diagnosis of AF was made based on the documentation of surface electrocardiograms, which showed a typical pattern of AF with an AF episode duration >30 s, whether asymptomatic or symptomatic.[21,22] Episodes detected by a wearable monitor or cardiac implantable electronic device were not included in the diagnosis of AF.[8]

Non-valvular AF was defined as the absence of moderate to severe mitral stenosis and an artificial mechanical mitral valve. The diagnosis of cardio-embolic stroke was confirmed by a neurologist at each institution according to the TOAST criteria,[23] and the TE in other organs was reviewed. Bleeding events, including major, clinically relevant non-major and minor ones according to the International Society on Thrombosis and Haemostasis scale, were also reviewed.[3,24]

### Statistical analysis

Normally distributed continuous variables are expressed as the mean and standard deviation, and categorical data are expressed as number and percentage. Nonparametrically distributed data are reported as the median of the interquartile range. For group comparisons, continuous variables were compared using Student's t-test or analysis of variance where appropriate, and categorical variables were analyzed using the chi-square test or Fisher's exact test as appropriate. The incidence rate of stroke, TE, and hemorrhagic events were calculated as the number of events per 100 person-years (P-Y), and reported separately in groups according to the ABCD score and ATT use. To evaluate the effect of ATT, the nearest-neighbor propensity matching was performed with the no ATT group as the control.[25]

To evaluate the performance of the proposed risk differentiation technique, receiver operating characteristic (ROC) analysis was performed. To compare the performance of different models, we compared two ROC curves according to the method described by DeLong, et al.[26] Using the non-gender $CHA_2DS_2$-VASc scoring model as a comparative benchmark, we evaluated the model performance of ABCD scores by calculating the C-statistics, continuous net reclassification improvement (NRI), and relative integrated differential improvement (IDI).[25,27,28] For survival analysis, Kaplan–Meier analysis and univariate and multivariate Cox regression analyses were performed. In the Cox proportional hazards survival model, we estimated the risk of stroke or TE associated with the non-antithrombotic group and the type of ATT. The Cox regression model was adjusted for basic characteristics, such as sex, age, HTN, DM, congestive heart failure, and vascular disease.

A $p$-value<0.05 was considered statistically significant. All statistical analyses were performed using R version 4.1.1 (Foundation for Statistical Computing, Vienna, Austria).

### Ethics statements

This study was approved by the Institutional Review Committee of each institution (IRB approval number 2005-018-19317). The authors declare that all supporting data are available within the article. The committee waived the need for patient consent due to the retrospective cohort study design. All procedures in this study involving human participants were performed in accordance with the ethical standards of institutions and/or national research committees.

## RESULTS

A total of 3001 non-valvular AF patients with non-gender $CHA_2DS_2$-VASc score 0–1 were recruited, and 2694 patients (mean age, 56.3±9.5 years; 26.9% female) with data related to ABCD score were finally analyzed. This study included 2694 patients with a non-gender $CHA_2DS_2$-VASc score 0–1 and non-valvular AF without prior stroke or TE. Among them, 1137 patients (42.2%) had a non-gender $CHA_2DS_2$-VASc score of 0, and 1557 patients (57.8%) had a non-gender $CHA_2DS_2$-VASc score of 1 (Table 1). Overall, 861 patients (32.0%) had an ABCD score of 0, and 1833 patients (68.0%) had an ABCD score of 1 or higher. Among patients with a non-gender $CHA_2DS_2$-VASc score 0–1, the number of patients receiving ATT was 2353 (87.3%). Among ATT regimens, NOACs were prescribed most commonly, followed by SAPT therapy, VKA therapy, and others [n=1040 (41.2%); n=661 (26.2%); n=423 (16.7%), respectively] (Supplemental Table 1, only online).

In the study cohort, 85 stroke or thromboembolic events occurred within 4.0±2.8 years and the 10104.27 P-Y follow-up period [annualized stroke incidence rate of total patients, 0.84/100 P-Y, 95% confidence interval (CI) 0.67–1.04] (Table 2). Patients without ATT with a non-gender $CHA_2DS_2$-VASc score 0–1 had an incidence rate of stroke or TE of 1.01/100 P-Y (95% CI 0.52–1.76). In patients treated with ATT adjusted by propensity score


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**Table 1.** Baseline Characteristics of Patients with Atrial Fibrillation for the Risk Prediction of Stroke or Thromboembolism (n=2694)

| Characteristics | Values |
|---|---|
| Age (yr) | 56.3±9.5 |
| Sex, female | 726 (26.9) |
| Non-gender $CHA_2DS_2$-VASc criteria | |
| Congestive heart failure | 194 (7.2) |
| Hypertension | 782 (29.0) |
| Age ≥65 years | 428 (15.9) |
| Diabetes mellitus | 115 (4.3) |
| Prior stroke | 0 (0.0) |
| Vascular disease | 38 (1.4) |
| Previous myocardial infarction | 18 (0.7) |
| Peripheral arterial disease | 8 (0.3) |
| Non-gender $CHA_2DS_2$-VASc=0 | 1137 (42.2) |
| Non-gender $CHA_2DS_2$-VASc=1 | 1557 (57.8) |
| ABCD score criteria | |
| Age ≥60 years | 1152 (42.8) |
| BNP/NT-proBNP | |
| BNP level ≥300 pg/mL | 239 (8.9) |
| NT-proBNP level ≥300 pg/mL | 155 (5.8) |
| Creatinine clearance <50 mL/min/1.73 $m^2$ | 112 (4.4) |
| Dimension of the LA ≥45 mm | 977 (39.5) |
| ABCD=0 | 861 (32.0) |
| ABCD≥1 | 1833 (68.0) |
| ATT | |
| No ATT | 341 (13.5) |
| SAPT therapy | 661 (26.2) |
| VKA therapy | 423 (16.7) |
| NOAC therapy | 1040 (41.2) |
| Apixaban | 279 (11.0) |
| Dabigatran | 187 (7.4) |
| Edoxaban | 326 (12.9) |
| Rivaroxaban | 246 (9.7) |
| Others* | 62 (2.3) |

$CHA_2DS_2$-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 sex category; ABCD, age ≥60 years, BNP level ≥300 pg/mL or NT-proBNP level ≥300 pg/mL, creatinine clearance <50 mL/min/1.73 $m^2$, dimension of the LA ≥45 mm; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LA, left atrium; ATT, antithrombotic therapy; SAPT, single anti-platelet; VKA, vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; DAPT, dual anti-platelet.
Data are presented as mean±standard deviation or n (%).
*Others include DAPT therapy, SAPT therapy with VKA therapy, SAPT therapy with NOAC therapy, and DAPT therapy with NOAC therapy.

matching, the incidence of stroke or TE was the lowest for SAPT therapy among all the ATT regimens (SAPT therapy, 0.39/100 P-Y, 95% CI 0.14–0.85; VKA therapy, 1.21/100 P-Y, 95% CI 0.72–1.91; NOAC therapy, 0.45/100 P-Y, 95% CI 0.26–0.72) (Table 2).

Regarding bleeding events, the crude incidence rate of bleeding was 1.19/100 P-Y in the no ATT group. Among all of the ATT regimens, VKA therapy was associated with the most bleeding events, and NOAC therapy was associated with the least bleeding events (SAPT therapy, 1.77/100 P-Y, 95% CI 1.15–2.59; VKA therapy, 6.70/100 P-Y, 95% CI 5.39–8.24; NOAC therapy, 1.55/100 P-Y, 95% CI 1.17–2.03).

Before applying the ABCD score, the overall stroke or TE rate in patients without ATT was 1.01 event/100 P-Y (95% CI 0.52–1.76); and after applying the ABCD score to the same group, the stroke or TE rate were 0.59/100 P-Y in patients with ABCD score of 0 and 1.55/100 P-Y in those with ABCD score ≥1 (Table 2). According to the ATT regimens used in patients with an ABCD score ≥1, the crude stroke incidence rate was the lowest in patients with NOAC therapy (SAPT therapy, 0.86/100 P-Y, 95% CI 0.32–1.87; VKA therapy, 1.25/100 P-Y, 95% CI 0.70–2.06; NOAC therapy, 0.44/100 P-Y, 95% CI 0.23–0.74). There were no significant differences in the incidence rate of stroke or TE events in patients with an ABCD score of 0 with or without NOAC therapy (0.59/100 P-Y, 95% CI 0.16–1.52 and 0.51/100 P-Y, 95% CI 0.14–1.31; $p$=0.888).

Since risk stratification was performed through ABCD score in the overall patient group, patients with ABCD score of 1 or higher showed more stroke and TE [hazard ratio (HR)=2.15, 95% CI 1.18–3.93, $p$=0.010] (Fig. 1). Even in patients who were not receiving ATT, patients with an ABCD score of 1 or higher showed a higher tendency for incidence of stroke and TE [HR 2.51 (95% CI 0.75–8.37, $p$=0.122] (Supplemental Fig. 1, only online). The area under curve of the ABCD score based on the ROC curve is shown in Fig. 2. The C-index of the ABCD score was 0.618 (95% CI 0.561–0.676), and that of the non-gender $CHA_2DS_2$-VASc score was 0.534 (95% CI 0.482–0.586). The C-index of the ABCD score was significantly superior to that of the non-gender $CHA_2DS_2$-VASc score (DeLong's test z=2.434; $p$=0.015). The continuous NRI of the ABCD score was significantly improved compared to that of the non-gender $CHA_2DS_2$-VASc score (continuous NRI=0.576, 95% CI 0.047–0.964; $p$=0.040) (Table 3). Even in patients not receiving ATT, continuous NRI of the ABCD score was significantly improved compared to the non-gender $CHA_2DS_2$-VASc score [continuous NRI=0.024, 95% CI 0.001–0.306; $p$=0.040] (Supplemental Table 2, only online). The IDI of the ABCD score showed improved discrimination power without statistical significance compared to that of the non-gender $CHA_2DS_2$-VASc score (IDI=0.033, 95% CI -0.006 to 0.174; $p$=0.066).

During the 10-year follow-up period, the cumulative incidence of stroke or TE was 5.4% (95% CI 4.0–6.8) in the overall patient cohort. In patients with an ABCD score of 0, there was no significant difference in the cumulative incidence of stroke or TE across all ATT regimens ($p$=0.074) (Fig. 3A). When ATT was administered in patients with an ABCD score ≥1, there was significantly low stroke or TE development in the NOAC group ($p$=0.003) (Fig. 3B). In Cox regression analysis, the risk of stroke or TE was significantly reduced by NOAC usage compared to no ATT usage (HR=0.30, 95% CI 0.14–0.66; $p$=0.002) (Fig. 4). In the detailed analysis according to the ABCD score,

**Table 2.** Stroke and Bleeding Events according to ABCD Score and Non-Gender $CHA_2DS_2$-VASc Score in Patients With or Without Individual Antithrombotic Treatment

| | n | Stroke or TE events | | | Bleeding event | | |
|---|---|---|---|---|---|---|---|
| | | Person-years | Events | Stroke or TE incidence rate, 100 person-years (95% CI) | Person-years | Events | Bleeding incidence rate, 100 person-year (95% CI) |
| Total patients | | | | | | | |
| Non-gender $CHA_2DS_2$-VASc=0–1 | 2465 | 10104.27 | 85 | 0.84 (0.67–1.04) | 9455.21 | 263 | 2.78 (2.46–3.14) |
| ABCD=0 | 786 | 3256.57 | 15 | 0.46 (0.26–0.76) | 3007.73 | 76 | 2.53 (1.99–3.16) |
| ABCD≥1 | 1679 | 6847.70 | 70 | 1.02 (0.80–1.29) | 6447.48 | 187 | 2.90 (2.50–3.35) |
| Non-gender $CHA_2DS_2$-VASc=0 | 1037 | 4248.69 | 30 | 0.71 (0.48–1.01) | 4047.34 | 92 | 2.27 (1.83–2.79) |
| ABCD=0 | 483 | 1953.23 | 8 | 0.41 (0.18–0.81) | 1846.35 | 35 | 1.90 (1.32–2.64) |
| ABCD≥1 | 554 | 2295.46 | 22 | 0.96 (0.60–1.45) | 2200.99 | 57 | 2.59 (1.96–3.36) |
| Non-gender $CHA_2DS_2$-VASc=1 | 1428 | 5855.58 | 55 | 0.94 (0.71–1.22) | 5407.87 | 171 | 3.16 (2.71–3.67) |
| ABCD=0 | 303 | 1303.34 | 7 | 0.54 (0.22–1.11) | 1161.38 | 41 | 3.53 (2.53–4.79) |
| ABCD≥1 | 1125 | 4552.24 | 48 | 1.05 (0.78–1.40) | 4246.49 | 130 | 3.06 (2.56–3.64) |
| None* | | | | | | | |
| Non-gender $CHA_2DS_2$-VASc=0–1 | 341 | 1190.61 | 12 | 1.01 (0.52–1.76) | 1089.86 | 13 | 1.19 (0.64–2.04) |
| ABCD=0 | 192 | 673.81 | 4 | 0.59 (0.16–1.52) | 628.89 | 4 | 0.64 (0.17–1.63) |
| ABCD≥1 | 149 | 516.80 | 8 | 1.55 (0.67–3.05) | 460.97 | 9 | 1.95 (0.89–3.71) |
| Non-gender $CHA_2DS_2$-VASc=0 | 207 | 726.63 | 6 | 0.83 (0.30–1.80) | 665.79 | 6 | 0.90 (0.33–1.96) |
| ABCD=0 | 140 | 502.84 | 3 | 0.60 (0.12–1.74) | 469.89 | 3 | 0.64 (0.13–1.87) |
| ABCD≥1 | 67 | 223.79 | 3 | 1.34 (0.28–3.92) | 195.90 | 3 | 1.53 (0.32–4.48) |
| Non-gender$CHA_2DS_2$-VASc=1 | 134 | 463.98 | 6 | 1.29 (0.47–2.81) | 424.07 | 7 | 1.65 (0.66–3.40) |
| ABCD=0 | 52 | 170.97 | 1 | 0.58 (0.01–3.26) | 159.00 | 1 | 0.63 (0.02–3.50) |
| ABCD≥1 | 82 | 293.01 | 5 | 1.71 (0.55–3.98) | 265.07 | 6 | 2.26 (0.83–4.93) |
| SAPT* | | | | | | | |
| Non-gender $CHA_2DS_2$-VASc=0–1 | 341 | 1535.66 | 6 | 0.39 (0.14–0.85) | 1472.64 | 26 | 1.77 (1.15–2.59) |
| ABCD=0 | 187 | 837.07 | 0 | 0.00 (0.00–0.44) | 785.72 | 11 | 1.40 (0.70–2.50) |
| ABCD≥1 | 154 | 698.59 | 6 | 0.86 (0.32–1.87) | 686.92 | 15 | 2.18 (1.22–3.60) |
| Non-gender $CHA_2DS_2$-VASc=0 | 213 | 958.65 | 1 | 0.10 (0.00–0.58) | 916.58 | 14 | 1.53 (0.84–2.56) |
| ABCD=0 | 138 | 589.15 | 0 | 0.00 (0.00–0.63) | 547.67 | 5 | 0.91 (0.30–2.13) |
| ABCD≥1 | 75 | 369.50 | 1 | 0.27 (0.01–1.51) | 368.91 | 9 | 2.44 (1.12–4.63) |
| Non-gender $CHA_2DS_2$-VASc=1 | 128 | 577.01 | 5 | 0.87 (0.28–2.02) | 556.06 | 12 | 2.16 (1.12–3.77) |
| ABCD=0 | 49 | 247.92 | 0 | 0.00 (0.00–1.49) | 238.05 | 6 | 2.52 (0.92–5.49) |
| ABCD≥1 | 79 | 329.09 | 5 | 1.52 (0.49–3.55) | 318.01 | 6 | 1.89 (0.69–4.11) |
| VKA* | | | | | | | |
| Non-gender $CHA_2DS_2$-VASc=0–1 | 341 | 1489.67 | 18 | 1.21 (0.72–1.91) | 1342.91 | 90 | 6.70 (5.39–8.24) |
| ABCD=0 | 59 | 287.60 | 3 | 1.04 (0.22–3.05) | 252.24 | 25 | 9.91 (6.41–14.63) |
| ABCD≥ 1 | 282 | 1202.07 | 15 | 1.25 (0.70–2.06) | 1090.67 | 65 | 5.96 (4.60–7.60) |
| Non-gender $CHA_2DS_2$-VASc=0 | 108 | 493.67 | 4 | 0.81 (0.22–2.07) | 454.87 | 27 | 5.94 (3.91–8.64) |
| ABCD=0 | 27 | 143.79 | 2 | 1.39 (0.17–5.02) | 135.38 | 10 | 7.39 (3.54–13.58) |
| ABCD≥1 | 81 | 349.88 | 2 | 0.57 (0.07–2.06) | 319.49 | 17 | 5.32 (3.10–8.52) |
| Non-gender $CHA_2DS_2$-VASc=1 | 233 | 996.00 | 14 | 1.41 (0.77–2.36) | 888.04 | 63 | 7.09 (5.45–9.08) |
| ABCD=0 | 32 | 143.81 | 1 | 0.70 (0.02–3.87) | 116.86 | 15 | 12.84 (7.18–21.17) |
| ABCD≥1 | 201 | 852.19 | 13 | 1.53 (0.81–2.61) | 771.18 | 48 | 6.22 (4.59–8.25) |
| NOAC* | | | | | | | |
| Non-gender $CHA_2DS_2$-VASc=0–1 | 1023 | 3768.07 | 17 | 0.45 (0.26–0.72) | 3476.63 | 54 | 1.55 (1.17–2.03) |
| ABCD=0 | 220 | 782.02 | 4 | 0.51 (0.14–1.31) | 710.83 | 10 | 1.41 (0.67–2.59) |
| ABCD≥ 1 | 803 | 2986.05 | 13 | 0.44 (0.23–0.74) | 2765.80 | 44 | 1.59 (1.16–2.14) |


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**Table 2.** Stroke and Bleeding Events according to ABCD Score and Non-Gender $CHA_2DS_2$-VASc Score in Patients With or Without Individual Antithrombotic Treatment (continued)

| | n | Stroke or TE events | | | Bleeding event | | |
|---|---|---|---|---|---|---|---|
| | | Person-years | Events | Stroke or TE incidence rate, 100 person-years (95% CI) | Person-years | Events | Bleeding incidence rate, 100 person-year (95% CI] |
| Non-gender $CHA_2DS_2$-VASc=0 | 336 | 1261.04 | 8 | 0.63 (0.27–1.25) | 1196.26 | 16 | 1.34 (0.76–2.17) |
| ABCD=0 | 116 | 403.69 | 2 | 0.50 (0.06–1.79) | 392.40 | 5 | 1.27 (0.41–2.97) |
| ABCD≥ 1 | 220 | 857.35 | 6 | 0.70 (0.26–1.52) | 803.86 | 11 | 1.37 (0.68–2.45) |
| Non-gender $CHA_2DS_2$-VASc=1 | 687 | 2507.03 | 9 | 0.36 (0.16–0.68) | 2280.37 | 38 | 1.67 (1.18–2.29) |
| ABCD=0 | 104 | 378.33 | 2 | 0.53 (0.06–1.91) | 318.43 | 5 | 1.57 (0.51–3.66) |
| ABCD≥1 | 583 | 2128.70 | 7 | 0.33 (0.13–0.68) | 1961.94 | 33 | 1.68 (1.16–2.36) |

CI, confidence interval; TE, thromboembolism; $CHA_2DS_2$-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 sex category; ABCD, age ≥60 years, BNP level≥300 pg/mL or NT-proBNP level≥300 pg/mL, creatinine clearance <50 mL/min/1.73 $m^2$, dimension of the left atrium ≥45 mm.
*Adjustment was performed between the groups of ATT by propensity score matching of variables (age, sex, congestive heart failure, hypertension, diabetes mellitus, and vascular disease).

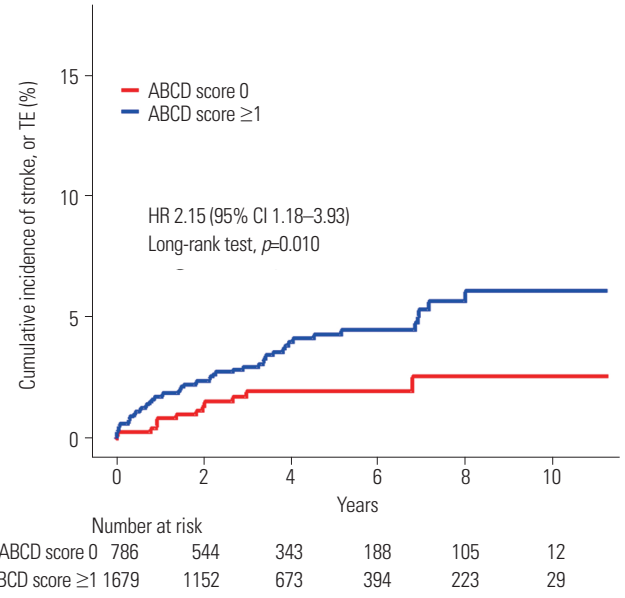


**Fig. 1.** Kaplan–Meier event curves for stroke/TE classified by ABCD score. Incidence of stroke and TE were significantly higher in all patients with an ABCD score of 1 or higher (HR 2.15, 95% CI 1.18–3.93, $p$=0.010). ABCD, age ≥60 years, BNP level ≥300 pg/mL or NT-proBNP level ≥300 pg/mL, creatinine clearance <50 mL/min/1.73 $m^2$, dimension of the left atrium ≥45 mm; HR, hazard ratio; CI, confidence interval; TE, thromboembolism.

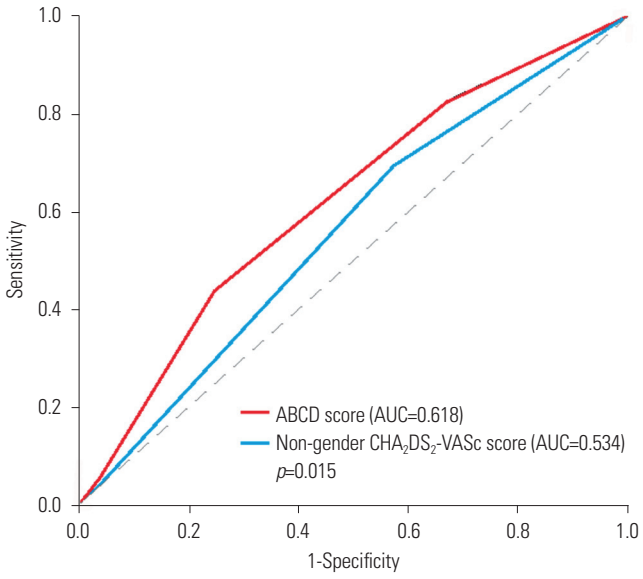


**Fig. 2.** Receiver operating characteristic curve of ABCD and non-gender $CHA_2DS_2$-VASc scores for stroke or thromboembolic risk. The C-index of the ABCD score is 0.618 (95% confidence interval 0.561–0.676), and the risk stratification of the ABCD score is superior to that of the $CHA_2SD_2$-VASc score ($p$=0.015). ABCD, age ≥60 years, BNP level ≥300 pg/mL or NT-proBNP level ≥300 pg/mL, creatinine clearance <50 mL/min/1.73 $m^2$, dimension of the left atrium ≥45 mm; AUC, area under the curve; $CHA_2DS_2$-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 sex category; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

NOAC usage in patients with an ABCD score of 0 did not show a significant difference in terms of stroke or TE frequency, but NOAC usage in patients with an ABCD score ≥1 significantly reduced stroke or TE compared to no ATT usage (HR=0.26, 95% CI 0.11–0.63; $p$=0.003).

## DISCUSSION

This study demonstrated the following important findings in Asian patients with AF who had low to intermediate stroke risks: 1) in patients with a non-gender $CHA_2DS_2$-VASc score 0–1, classified as low to intermediate stroke risk group, a substantial number of stroke and TE events were observed, which indicates an unmet need for a further risk stratification scheme in these patients; 2) the ABCD score was superior to the non-gender

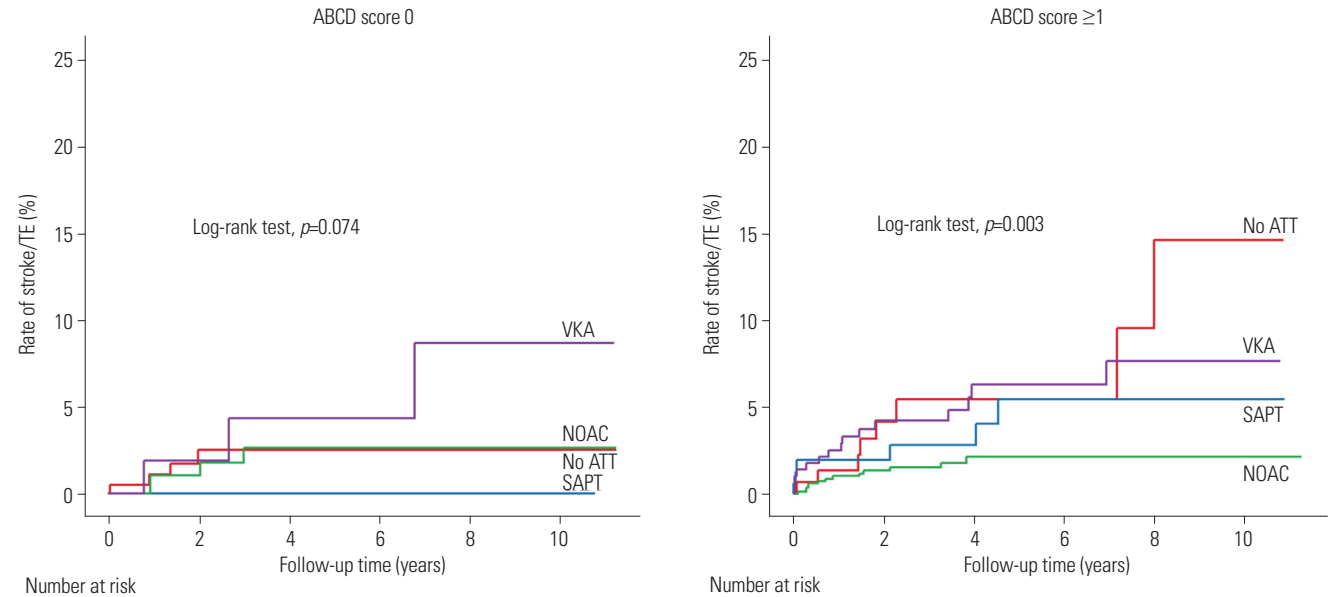


**Fig. 3.** Kaplan–Meier event curves for stroke/TE classified by ABCD score and ATT. (A) Cumulative incidence of stroke or TE in patients with an ABCD score of 0 is shown, and there is no significant difference in the rate of stroke or TE between the ATTs (log-rank test, $p$=0.074). (B) Cumulative incidence of stroke or TE in patients with an ABCD score ≥1 is shown, and the rate of stroke or TE is significantly low in the NOAC group (log-rank test, $p$=0.003). ABCD, age ≥60 years, BNP level ≥300 pg/mL or NT-proBNP level ≥300 pg/mL, creatinine clearance <50 mL/min/1.73 m$^2$, 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; TE, thromboembolism.

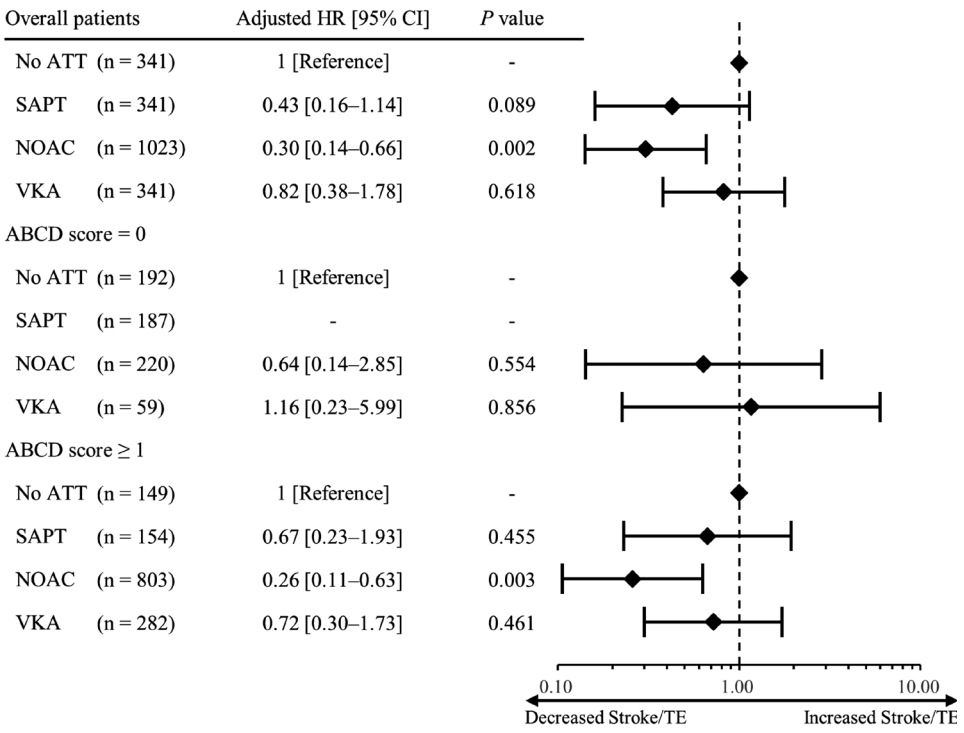


**Fig. 4.** Forest plot of HR for the association of ATTs. Adjustments were made for age, sex, hypertension, diabetes mellitus, congestive heart failure, and vascular disease. In the SAPT group with an ABCD score of 0, no stroke event occurred during the study period, which made the calculation of the hazard ratio impossible. HR, hazard ratio; ABCD, age ≥60 years, BNP level ≥300 pg/mL or NT-proBNP level ≥300 pg/mL, creatinine clearance <50 mL/min/1.73 m$^2$, 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; TE, thromboembolism; NT-proBNP, N-terminal pro-B-type natriuretic peptide.


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**Table 3.** C-index, Continuous IDI, and NRI of ABCD Score Compared to Non-Gender $CHA_2DS_2$-VASc Score

| | Non-gender $CHA_2DS_2$-VASc score | 95% CI | ABCD score | 95% CI | *p* value |
|---|---|---|---|---|---|
| C-index | 0.534 | 0.482–0.586 | 0.618 | 0.561–0.676 | 0.015 |
| Continuous NRI* | - | - | 0.576 | 0.047–0.964 | 0.040 |
| IDI* | - | - | 0.033 | -0.006–0.174 | 0.066 |

$CHA_2DS_2$-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 sex category; CI, confidence interval; ABCD, age ≥60 years, BNP level ≥300 pg/mL or NT-proBNP level ≥300 pg/mL, creatinine clearance <50 mL/min/1.73 $m^2$, dimension of the left atrium ≥45 mm; NRI, net reclassification index; IDI, integrated discriminatory improvement; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*For comparison with non-gender $CHA_2DS_2$-VASc score.

$CHA_2DS_2$-VASc score in identifying truly low stroke risk patients who do not benefit from ATT; 3) a large proportion of patients with low to intermediate stroke risk were prescribed ATT in real-world clinical practice (ATT, 87.3% of overall patients); and 4) stratification using the ABCD score showed a potential benefit in implementing ATT with NOAC therapy.

A non-gender $CHA_2DS_2$-VASc score 0–1 is classified as low to intermediate risk, and current guidelines recommend no ATT or consider anticoagulation according to a given patient's risk factors other than $CHA_2DS_2$-VASc risk factors.[6,8] Although a substantial number of low to intermediate risk patients were exposed to some residual stroke risk (1.61/100 P-Y, 95% CI 0.00–3.23), anticoagulation without detailed risk stratification failed to show a net clinical benefit from ATT.[29-32]

In this respect, the ABCD score, comprising enforced age criteria and biomarkers reflecting residual stroke risk, which can be overlooked within simple clinical risk stratification schemes, such as the $CHA_2DS_2$-VASc score, can help in the detailed risk stratification of AF patients with low to intermediate stroke risk. This study's findings were consistent with those of recent studies, which showed that a combination of such biomarkers and imaging factors are superior to the $CHA_2DS_2$-VASc score in identifying truly low risk patients who do not require ATT. Indeed, age of 60–64 years (HR, 1.20; 95% CI 1.13–1.27),[33] NT-proBNP level (HR 2.35; 95% CI 1.62–3.40),[12] creatinine clearance (HR 1.09; 95% CI 1.04–1.13),[13] and anatomical remodeling of the LA[34,35] were contributing factors for stroke risk. Unlike the $CHA_2DS_2$-VASc score, which consists of only clinical risk factors, the ABCD score includes two blood biomarkers and one imaging biomarker that can be easily obtained in clinical practice and can help in the detailed risk stratification of AF patients with a truly low stroke risk.

One more noteworthy observation of this study is that a substantial number of patients with a low to intermediate risk of AF were treated with ATT in real-world clinical practice in Korea. This may suggest that clinicians are concerned about residual stroke risk, which cannot be appropriately assessed by the $CHA_2DS_2$-VASc score. Additionally, more ischemic strokes occur in East Asian patients with AF than in Western patients, and this may affect ATT usage.[36] Furthermore, the criteria for ATT in the previous $CHA_2DS_2$-VASc score were initially developed in the era of VKA therapy, but the current treatment standards should be adjusted based on the differences made by the introduction of NOACs, which showed an improved safety profile and a low risk of intracranial bleeding.[29] Therefore, the introduction of NOACs has made ATT more effective and safer for patients with AF at low to intermediate risk of stroke.

For patients with risk factors based on the ABCD score (i.e., ≥1), the use of NOACs was superior to anti-platelet agents and VKAs in reducing stroke risk in AF patients with low to intermediate risk of stroke or TE. In a previous study that compared aspirin and apixaban in patients with a $CHA_2DS_2$-VASc score of 1, apixaban lowered the stroke incidence.[37] In a United States cohort study of patients with a $CHA_2DS_2$-VASc score 0–1, there were no significant differences in the stroke risk between apixaban, rivaroxaban, and dabigatran.[38] However, patients at low to intermediate risk of stroke appeared to have a net clinical disadvantage from VKA treatment.[31] Therefore, the refined use of NOACs in patients with detailed risk stratification (ABCD score of 1 or more) may further reduce the risk of stroke among low to intermediate risk patients with AF.[6,8] It should be noted that stroke prevention is only one aspect of the holistic or integrated healthcare approach to AF based on the Atrial fibrillation Better Care pathway.[39] The latter has been recommended in international guidelines,[5,8] especially since adherence with such an integrated healthcare approach is associated with improved clinical outcomes.[40,41]

A limitation of this retrospective analysis study was the small number of patients with stroke events. However, this did not undermine the ABCD score's ability to discriminate low-risk patients for stroke or TE prevention among those with AF. Additionally, since this study was conducted in only Korean patients, the results cannot be applied to other ethnicities; therefore, additional studies with other ethnicities are required. The individual stroke risk in AF patients has a dynamic nature that changes over time, which is associated with ageing and incident comorbidities. Since this study was conducted with retrospective analysis, it was difficult to obtain dynamic changes in ABCD scores and $CHA_2DS_2$-VASc scores at a specific time point after the baseline. Further studies are needed to ascertain the changes in the ABCD score over time. In addition, a future study on net clinical benefit considering the balance between the stroke risk and the bleeding risk should be performed.

In conclusion, this study provides a method to further refine stroke risk stratification in patients with AF who are clinically defined as having low to intermediate risk with the combination of clinical risk factors and biomarkers. The biomarker-based ABCD score demonstrated improved stroke risk stratification in AF patients with a non-gender $CHA_2DS_2$-VASc score 0–1. Additionally, NOAC use and an ABCD score ≥1 was associated

with significantly lower ischemic stroke in AF patients with a non-gender $CHA_2DS_2$-VASc score 0–1.

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## AUTHOR CONTRIBUTIONS

Conceptualization: Gregory Y.H. Lip and Seung Yong Shin. Data curation: Kyeongmin Byeon, Ki-Woon Kang, Yae Min Park, You Mi Hwang, Sung Ho Lee, Eun-Sun Jin, Seung-Young Roh, Jin Seok Kim, Jinhee Ahn, So-Ryoung Lee, Eue-Keun Choi, Min-soo Ahn, Eun Mi Lee, Hwan-Cheol Park, Ki Hong Lee, Min Kim, Joon Hyouk Choi, and Jum Suk Ko. Formal analysis: Moonki Jung. Funding acquisition: Seung Yong Shin, Jin Bae Kim, and Changsoo Kim. Investigation: Gregory Y.H. Lip and Seung Yong Shin. Methodology: Moonki Jung and Seung Yong Shin. Project administration: Seung Yong Shin and Jin Bae Kim. Resources: Moonki Jung and Seung Yong Shin. Software: Moonki Jung and Seung Yong Shin. Supervision: Gregory Y.H. Lip and Seung Yong Shin. Validation: Jin Bae Kim and Changsoo Kim. Visualization: Moonki Jung and Seung Yong Shin. Writing—original draft: Moonki Jung and Seung Yong Shin. Writing—review & editing: Gregory Y.H. Lip and Seung Yong Shin. Approval of final manuscript: all authors.

## ORCID iDs

| | |
|---|---|
| Moonki Jung | https://orcid.org/0000-0002-9935-7725 |
| Kyeongmin Byeon | https://orcid.org/0000-0001-9037-381X |
| Ki-Woon Kang | https://orcid.org/0000-0002-1361-0022 |
| Yae Min Park | https://orcid.org/0000-0003-3597-9768 |
| You Mi Hwang | https://orcid.org/0000-0001-8385-6485 |
| Sung Ho Lee | https://orcid.org/0000-0002-1018-7871 |
| Eun-Sun Jin | https://orcid.org/0000-0003-1182-8244 |
| Seung-Young Roh | https://orcid.org/0000-0002-0854-9079 |
| Jin Seok Kim | https://orcid.org/0000-0002-1854-9312 |
| Jinhee Ahn | https://orcid.org/0000-0001-6179-1254 |
| So-Ryoung Lee | https://orcid.org/0000-0002-6351-5015 |
| Eue-Keun Choi | https://orcid.org/0000-0002-0411-6372 |
| Min-soo Ahn | https://orcid.org/0000-0001-7896-8175 |
| Eun Mi Lee | https://orcid.org/0000-0002-2447-9453 |
| Hwan-Cheol Park | https://orcid.org/0000-0002-9258-0481 |
| Ki Hong Lee | https://orcid.org/0000-0002-9938-3464 |
| Min Kim | https://orcid.org/0000-0002-8132-9873 |
| Joon Hyouk Choi | https://orcid.org/0000-0003-4245-1582 |
| Jum Suk Ko | https://orcid.org/0000-0002-8573-0066 |
| Jin Bae Kim | https://orcid.org/0000-0002-0293-0901 |
| Changsoo Kim | https://orcid.org/0000-0002-5940-5649 |
| Gregory Y.H. Lip | https://orcid.org/0000-0002-7566-1626 |
| Seung Yong Shin | https://orcid.org/0000-0002-3408-6899 |

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