

Atrial Cardiopathy Worsens Neurological Severity, Raises Recurrence Rates, and Leads to Poor Vascular Outcomes in Patients With Embolic Stroke of Undetermined Source

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Background and Purpose Atrial cardiopathy (AC) has been studied for its significance in embolic stroke of undetermined source (ESUS). This real-world study examines the relevance of AC in ESUS and its impact on stroke severity, recurrence, and major adverse cardiovascular events (MACEs).

Methods We analyzed patients from stroke registries of South Korean centers (2014–2019) aged ≥ 20 years with acute ESUS or cardiogenic stroke without a definite embolic source. AC was defined by left atrial (LA) enlargement (diameter >40 mm in men and >38 mm in women; or LA volume index >34 mL/m²) or elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP, ≥ 250 pg/mL) levels. Patients were classified based on AC presence and stratified by the number of

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factors (AC groups 0, 1, and 2). Survival analysis in original and propensity score (PS)-matched cohorts assessed the impact of AC on stroke severity and vascular outcomes.

Results Among 5,787 patients (65.9 ± 13.9 years; female: 39.8%), 45.0% met the AC criteria (group 1: 40.3%, group 2: 4.7%). In the original cohort, AC group 2 was associated with increased stroke recurrence (hazard ratio [HR]: 1.76, 95% confidence interval [CI]: 1.06–2.92, $P=0.03$). After PS-matching, stroke recurrence remained significantly increased for AC (HR: 1.37, 95% CI: 1.04–1.79, $P=0.02$) and group 2 (HR: 1.94, 95% CI: 1.16–3.26, $P=0.01$). MACE outcomes increased in the group 2 patients (HR: 1.70, 95% CI: 1.07–2.70, $P=0.02$). NT-proBNP (HR: 0.97, 95% CI: 0.84–1.12, $P=0.69$) or LA enlargement (HR: 1.15, 95% CI: 0.89–1.49, $P=0.28$) alone were not predictive. AC correlated with longer hospital stays, and AC stratification with higher severity.

Conclusion Especially with multiple factors, AC was associated with adverse clinical outcome in patients with ESUS. These findings underscore the importance of AC stratification in the management of ESUS patients.

Keywords Atrial cardiopathy; Atrial remodeling; Cardiomyopathies; Ischemic stroke; Major adverse cardiovascular event; Cardiovascular diseases

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Introduction

The emergence of embolic strokes of undetermined source (ESUS) marked a shift in the management of cryptogenic strokes.¹ Considering its embolic nature, various potential causes are suspected. Atrial cardiopathy (AC) reportedly plays a significant role in embolic strokes.^{2,3} Various studies have explored whether the presence of AC affects clinical outcomes. However, studies exploring whether the use of anticoagulants favors the use of antiplatelets^{3–5} have exhibited neutral results in preventing recurrent strokes.

AC is characterized by structural and electrical abnormalities in the atria.^{2,6} Current evidence suggests that AC may be an indicator of stroke incidence.^{7,8} However, knowledge gaps still need to be addressed. The clinical significance of AC in stroke recurrence and vascular outcomes should be prioritized, particularly in the context of large-scale population data and comprehensive follow-ups.

We aimed to address this gap by analyzing comprehensive multicenter data on stroke patients with ESUS. We investigated the differences in stroke outcomes, including recurrent stroke, vascular outcomes, and stroke severity, based on the presence of AC.

Methods

Study design and patients

Our study aimed to examine the prevalence of ESUS and analyze factors associated with stroke severity and recurrence. The

real-world study of the embolic stroke of undetermined sources (ROS-ESUS) cohort was named based on its construction and comprised patients who were admitted to each stroke center between January 2014 and December 2019 with ischemic strokes classified as ESUS. This nationwide study, encompassing 20 centers, received approval from the institutional review boards of all participating institutions in 2022. ROS-ESUS cohort enrollment was considered based on the presence of non-lacunar infarction occurring within 7 days in patients aged ≥ 20 years with undetermined etiology, under the criteria of Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification as follows: negative evaluation (or cryptogenic stroke) or cardioembolism, but not high-risk cardioembolic sources.^{9,10} The overall ESUS classification was determined by physicians at each stroke center, and all patients classified as having ESUS were consecutively enrolled in the ROS-ESUS cohort.

The exclusion criteria included: (1) patients diagnosed with atrial fibrillation, (2) those with active cancer, (3) those with high risk of cardioembolism, (4) those with last normal time of 7 days or more, and (5) those who the attending physician determined that the patient is not an appropriate candidate based on clinical judgment. Detailed clinical imaging (transthoracic echocardiography) and laboratory data were collected from each center. The inclusion flowchart is shown in Figure 1.

Patients who met the eligibility criteria were followed up at 3 months, 1 year, and beyond 1 year after their diagnosis of ESUS. Follow-up was discontinued in cases of loss to follow-up or death. Although the maximum follow-up duration varied slightly across institutions, most patients were followed up until 2023, when

possible.

The study design was approved by the Institutional Review Board of Samsung Medical Center (IRB No. SMC-2022-02-010). Due to its retrospective nature, the requirement for written informed consent was waived.

Defining AC

AC was defined based on the presence of either of the following criteria: (1) atrial enlargement was defined as having a left atrial (LA) diameter exceeding 40 mm for men and 38 mm for women on echocardiography (parasternal long axis view) performed during the time of admission by each institute.¹¹ In addition, participants with LA volume index exceeding 34 mL/m² were classified as having atrial enlargement,¹² and (2) elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels of ≥ 250 pg/mL during admission were considered indicative of

atrial dysfunction.¹³ We also classified each individual according to the number of criteria they met. They were grouped not only by the presence of AC (AC and non-AC groups) but also by the number of factors that were satisfied (groups 0, 1, and 2). Patients without NT-proBNP measurements ($n=3,845$) and echocardiographic features ($n=695$) were classified as not meeting the diagnostic criteria.

Vascular outcomes and stroke severity

The primary outcome of this study was the time-to-first recurrent ischemic stroke. Patients with hemorrhagic strokes, transient ischemic attacks (TIAs), or strokes of unidentifiable type were excluded. The time-to-major adverse cardiovascular events (MACEs) was the secondary outcome. MACE comprised recurrent ischemic stroke, hemorrhagic stroke, symptomatic heart failure, myocardial infarction, and vascular death.

Ischemic stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) scores, changes in modified Rankin Scale (mRS) scores, and the length of hospital stay was also analyzed.

Statistical analysis

Statistical analyses were conducted using R (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria) and Python (version 3.12.4; <https://www.python.org/>), with a significance threshold set at $P<0.05$. Baseline characteristics between groups, categorized by the presence of AC, were compared using the chi-square test and the Mann-Whitney U test. Kaplan-Meier survival analysis, along with log-rank tests, was performed to assess the survival probability between AC groups. Competing risk analysis was then employed with the Fine-Gray model to compare outcomes of recurrent strokes and MACEs while accounting for unrelated deaths. The covariates considered were age, sex, and body mass index (BMI), along with medical history of stroke, TIAs, peripheral arterial disease, coronary heart disease, hypertension, diabetes mellitus, dyslipidemia, and smoking status, which were selected as prominent risk factors for stroke.¹⁴ They were then independently subjected to regression analysis to assess vascular outcomes, and those meeting the $P<0.10$ were primarily considered for each multivariate analysis. Although most collected data were not modified, BMI measurements out of three standard deviation ranges were substituted with the median values. Age and BMI data were standard-scaled for statistical analyses, and missing data for covariates were rare and were therefore excluded from the statistical analysis.

Stroke severity was assessed using NIHSS scores at admission (baseline) and discharge. For analysis, severity levels were classified into three groups: mild (0–4), moderate (5–14), and severe

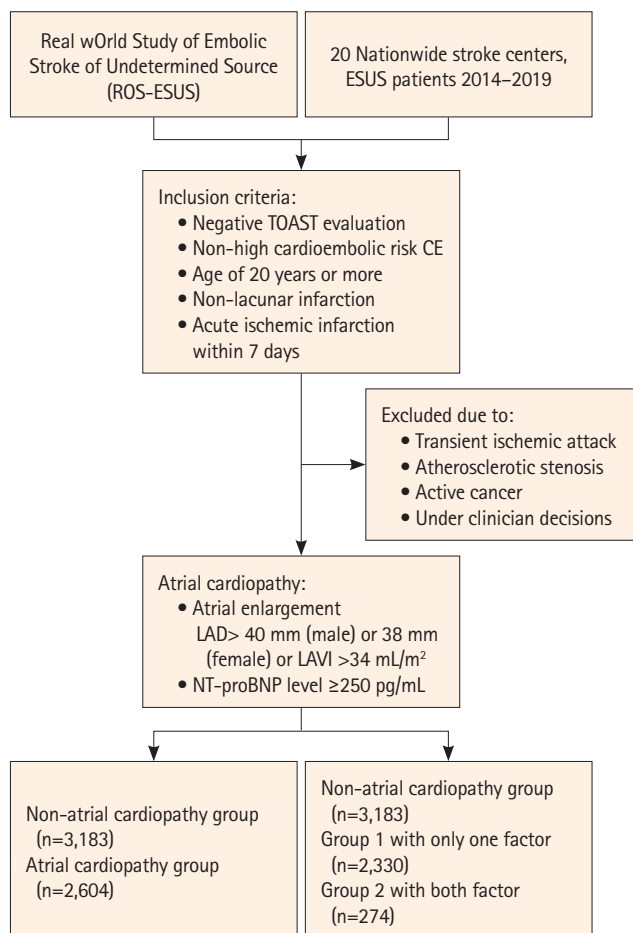


Figure 1. Inclusion flowchart of the real-world study of embolic stroke of undetermined source (ROS-ESUS) cohort. Patients were selected from stroke registries across all participating centers and were subsequently screened based on inclusion and exclusion criteria. Finally, they were classified according to the presence or absence of atrial cardiopathy. TOAST, Trial of Org 10172 in Acute Stroke Treatment; CE, cardioembolism; LAD, left atrial diameter; LAVI, left atrial volume index; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

(≥ 15), and comparisons were conducted using chi-square tests and residual heatmaps. Ordinal variables, including NIHSS scores and mRS scores, were analyzed by comparing medians and interquartile range (IQR), while continuous variable, length of hospitalization, was analyzed by comparing means and standard deviations. Mann-Whitney U or Kruskal-Wallis H tests were applied, followed by Dunn's test with Bonferroni correction when necessary. Two patients without admission NIHSS scores were excluded from the analysis, and hospitalized days outside of the three standard deviation ranges were substituted with the median value.

A propensity score (PS)-matched dataset was created to ensure balance between the AC and non-AC groups. The PS was derived using a multivariate logistic regression model including age, sex, BMI, admission NIHSS score, CHA₂DS₂-VASc score, and medical history variables such as congestive heart failure, hypertension, diabetes mellitus, history of TIA and stroke, peripheral arterial disease, coronary heart disease, dyslipidemia, and smoking, as independent predictors. Blood pressure, pulse rate, presence of atrial fibrillation during admission, and use of antiplatelet agents or oral anticoagulants at discharge were also recorded. The variables were carefully selected to maximize randomization after reviewing factors associated with stroke recurrence.¹⁵ Missing values (less than 1%) were replaced with the median value of each variable. PSM was performed using the nearest-neighbor method with 1:1 matching within a caliper of 0.12. The performance of PS matching was assessed by quantifying the absolute standardized differences in patient characteristics (Supplementary Figure 1). After, univariate Cox regression was performed to compare the AC and non-AC groups, as well as the stratified groups. Finally, sensitivity analysis was employed to determine the trends in recurrent ischemic stroke. All graphs exhibited linear trends in both directions or parabolic trends. Although the significance was mixed, as the presence of AC alone shows marginal significance, the result was consequential to the stratified group sensitivity with strong significance. Therefore, the tendency was numerically comparable.

Results

Baseline characteristics

Among the 5,787 patients investigated, the mean age and BMI were 65.9 ± 13.9 years (female 39.8%) and 23.7 ± 3.2 , respectively. While 2.1% of patients had a history of TIA, 19.0% had a history of stroke, including hemorrhagic stroke. Comorbidities included hypertension (61.1%), diabetes mellitus (29.5%), dyslipidemia (39.6%), coronary heart disease (10.8%), peripheral arterial disease (1.3%), and current smoking status (26.7%).

The ratios for each condition varied, as 8.7% of the patients had NT-proBNP level ≥ 250 pg/mL, and 41.1% had LA enlargement based on an increased LA diameter or volume index. A total of 45.0% of patients satisfied our definition of AC, and groups 0, 1, and 2 accounted for 55.0%, 40.3%, and 4.7%, respectively. NIHSS scores at admission and discharge were 3 (1–6) and 2 (0–4), respectively. The average follow-up duration was 16.1 ± 19.1 months, with a maximum of 107.9 months. During this period, 246 patients experienced a recurrent ischemic stroke, and 306 patients had a MACE event (Supplementary Table 1). Comparison between the AC and non-AC groups is presented in Table 1.

Recurrent vascular events in the AC group in the original cohort

The Kaplan-Meier curves showed a marginal difference between the AC and non-AC groups for recurrent stroke ($P=0.05$). When stratified, group 2 was responsible for greater increase in hazard ratio (HR) ($P=0.04$) compared to the other groups (Supplementary Figure 2A and B). When unrelated deaths were considered, the AC group exhibited borderline significance in ischemic stroke recurrence in univariate (HR: 1.26, 95% confidence interval [CI]: 0.98–1.62, $P=0.07$) and multivariate (HR: 1.25, 95% CI: 0.97–1.60, $P=0.08$) assays. Moreover, while group 1 exhibited low significance in univariate (HR: 1.20, 95% CI: 0.93–1.56, $P=0.16$) and multivariate (HR: 1.19, 95% CI: 0.92–1.55, $P=0.18$) analyses, group 2 displayed compelling results in both univariate (HR 1.75, 95% CI: 1.06–2.89, $P=0.03$) and multivariate (HR: 1.76, 95% CI: 1.06–2.92, $P=0.03$) models (Table 2).

However, the MACE outcomes were contradictory. The Kaplan-Meier curves also exhibited marginal significance in the AC and non-AC groups ($P=0.05$), whereas group 2 displayed a larger difference ($P=0.03$) (Supplementary Figure 2C and D). However, in the subdistribution hazard analysis, all the results were not significant (all $P>0.05$), even in the stratified group 2 (univariate HR: 1.56, 95% CI: 0.96–2.52, $P=0.07$) (Table 2).

Survival analysis after PS matching

After PS matching, 2,604 pairs were selected, exhibiting a notable increase in the risk of ischemic stroke in the AC group ($P=0.02$) and stratified AC group 2 ($P=0.01$) (Table 2). The difference between curves increased in the original cohort. In MACE, an early phase overlap existed in the AC group versus the non-AC group ($P=0.11$), but stratified AC group 2 was similar to the ischemic stroke results ($P=0.02$) (Figure 2).

HR for the AC group was estimated and exhibited significance in ischemic stroke recurrence (HR: 1.37, 95% CI: 1.04–1.79, $P=0.02$), but not with MACE (HR: 1.21, 95% CI: 0.96–1.53, $P=0.11$),

which was consistent with competing risk analysis models. The AC group was evaluated after stratification into groups 1 and 2. When measured in the PS matched cohort, the significance in

ischemic stroke recurrence escalated in groups 1 (HR: 1.30, 95% CI: 0.99–1.73, $P=0.06$) and 2 (HR: 1.94, 95% CI: 1.16–3.26, $P=0.01$), although group 1 exhibited borderline significance. MACE

Table 1. Characteristics of AC group and non-AC group before and after propensity score matching

	Original cohort			PS-matched cohort		
	AC group (n=2,604)	Non-AC group (n=3,183)	P^*	Matched AC group (n=2,604)	Matched non-AC group (n=2,604)	P^*
Age (yr)	68.58±12.89	63.70±14.27	<0.01	68.58±12.89	68.67±12.57	0.96
Female sex	1,200 (46.01)	1,145 (35.97)	<0.01	1,200 (46.01)	1,154 (44.32)	0.89
Body mass index (kg/m ²)	24.02±3.20	23.49±3.15	<0.01	24.02±3.20	24.05±3.24	0.90
Vascular risk factors						
Peripheral arterial disease	31 (1.19)	43 (1.35)	0.71	31 (1.19)	37 (1.42)	0.25
Coronary heart disease	374 (14.36)	253 (7.95)	<0.01	374 (14.36)	380 (14.59)	0.84
Hypertension	1,770 (67.97)	1,763 (55.39)	<0.01	1,770 (67.97)	1,805 (69.32)	0.31
Diabetes mellitus	812 (31.18)	894 (28.09)	0.01	812 (31.18)	793 (30.45)	0.59
Dyslipidemia	1,036 (39.78)	1,255 (39.43)	0.80	1,036 (39.78)	1,049 (40.28)	0.73
Current smoker	589 (22.62)	956 (30.03)	<0.01	589 (22.62)	538 (20.66)	0.09
Previous TIA	45 (1.73)	74 (2.32)	0.13	45 (1.73)	32 (1.23)	0.17
Previous stroke	474 (18.20)	624 (19.60)	0.12	474 (18.20)	487 (18.70)	0.67
Ischemic stroke recurrence	123 (4.72)	123 (3.86)	0.12	123 (4.72)	91 (3.49)	0.03
MACE	152 (5.84)	154 (4.84)	0.10	152 (5.84)	126 (4.84)	0.12
Admission NIHSS score	3 (1–6)	3 (1–6)	0.86	3 (1–6)	2 (1–6)	0.13
Discharge NIHSS score	1 (0–4)	2 (0–4)	0.42	1 (0–4)	2 (0–4)	0.60
Details of AC						
NT-proBNP	928±3,524 (n=992)	70.80±59.00	<0.01	928±3,524 (n=992)	79.34±59.65 (n=819)	<0.01
LAD (mm)	41.14±5.67 (n=2,522)	34.02±3.90	<0.01	41.14±5.67 (n=2,522)	34.17±3.89 (n=2,068)	<0.01
LAVI (mm/m ²)	40.74±14.47 (n=1,831)	24.56±5.89	<0.01	40.74±14.47 (n=1,831)	24.87±6.03 (n=1,213)	<0.01
Months to recurrence	15.50±17.93	16.61±20.04	0.06	15.50±17.93	15.73±18.53	0.26
Months to MACE	15.41±17.79	16.45±19.91	0.08	15.41±17.79	15.54±18.36	0.39

Values are presented as mean±standard deviation, n (%), or median (interquartile range). The medians and interquartile ranges of the AC and non-AC groups were compared using Mann-Whitney U tests.

AC, atrial cardiopathy; PS, propensity score; TIA, transient ischemic attack; MACE, major adverse cardiovascular event; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LAD, left atrial diameter; LAVI, left atrial volume index.

P -values were calculated to compare AC and non-AC groups in the original* and propensity score-matched cohorts.[†]

Table 2. Effect of AC on vascular outcomes

	Original cohort (n=5,787)				PS-matched cohort (n=5,208)	
	Univariate		Multivariate		HR (95% CI)	<i>P</i>
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>		
Recurrent ischemic stroke						
Non-AC vs. AC	1.26 (0.98–1.62)	0.07	1.25 (0.97–1.60)	0.08	1.37 (1.04–1.79)	0.02
AC group 0	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
AC group 1	1.20 (0.93–1.56)	0.16	1.19 (0.92–1.55)	0.18	1.30 (0.99–1.73)	0.06
AC group 2	1.75 (1.06–2.89)	0.03	1.76 (1.06–2.92)	0.03	1.94 (1.16–3.26)	0.01
MACE						
Non-AC vs. AC	1.19 (0.95–1.50)	0.14	1.16 (0.92–1.47)	0.22	1.21 (0.96–1.53)	0.11
AC group 0	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–
AC group 1	1.15 (0.91–1.47)	0.25	1.13 (0.88–1.44)	0.34	1.16 (0.91–1.48)	0.24
AC group 2	1.56 (0.96–2.52)	0.07	1.44 (0.89–2.35)	0.14	1.70 (1.07–2.70)	0.02

PS, propensity score; HR, hazard ratio; CI, confidence interval; AC, atrial cardiopathy; MACE, major adverse cardiovascular event.

outcomes were statistically meaningful in group 2 (HR 1.70, 95% CI: 1.07–2.70, $P=0.02$), unlike the previous results in the original cohort.

Stroke severity difference at admission and discharge stratified by AC

There was no significant difference in stroke severity (mild, moderate, or severe) at baseline or discharge between the AC and non-AC groups ($P>0.05$) (Figure 3). However, elevated NT-proBNP levels (Spearman's rank correlation: $\rho=0.12$, $P<0.05$) and LA enlargement (median NIHSS score: 3 in patients without LA enlargement vs. 2 in those with enlargement; $P<0.05$ by Mann-Whitney U test) were both significantly associated with NIHSS.

In addition, when the groups were stratified according to the number of AC factors, the effects of the non-AC, AC, and Group 1 groups were mixed, and group 2 displayed a clear correlation with stroke severity (Supplementary Figure 3). No difference in NIHSS score existed between non-AC and AC groups. However, when the AC group was stratified by the number of factors, group 2 surpassed the non-AC group and group 1 in terms of severity during admission (difference in median was both +2, $P<0.05$) and discharge (difference in median was both +1, $P<0.05$), whereas group 1 exhibited no difference compared to the non-AC group. Notably, hospitalization stays differed in trends. The AC group surpassed the non-AC group in hospital stays by 0.38 days ($P<0.05$), and group 1 patients exhibited longer hospital stays than

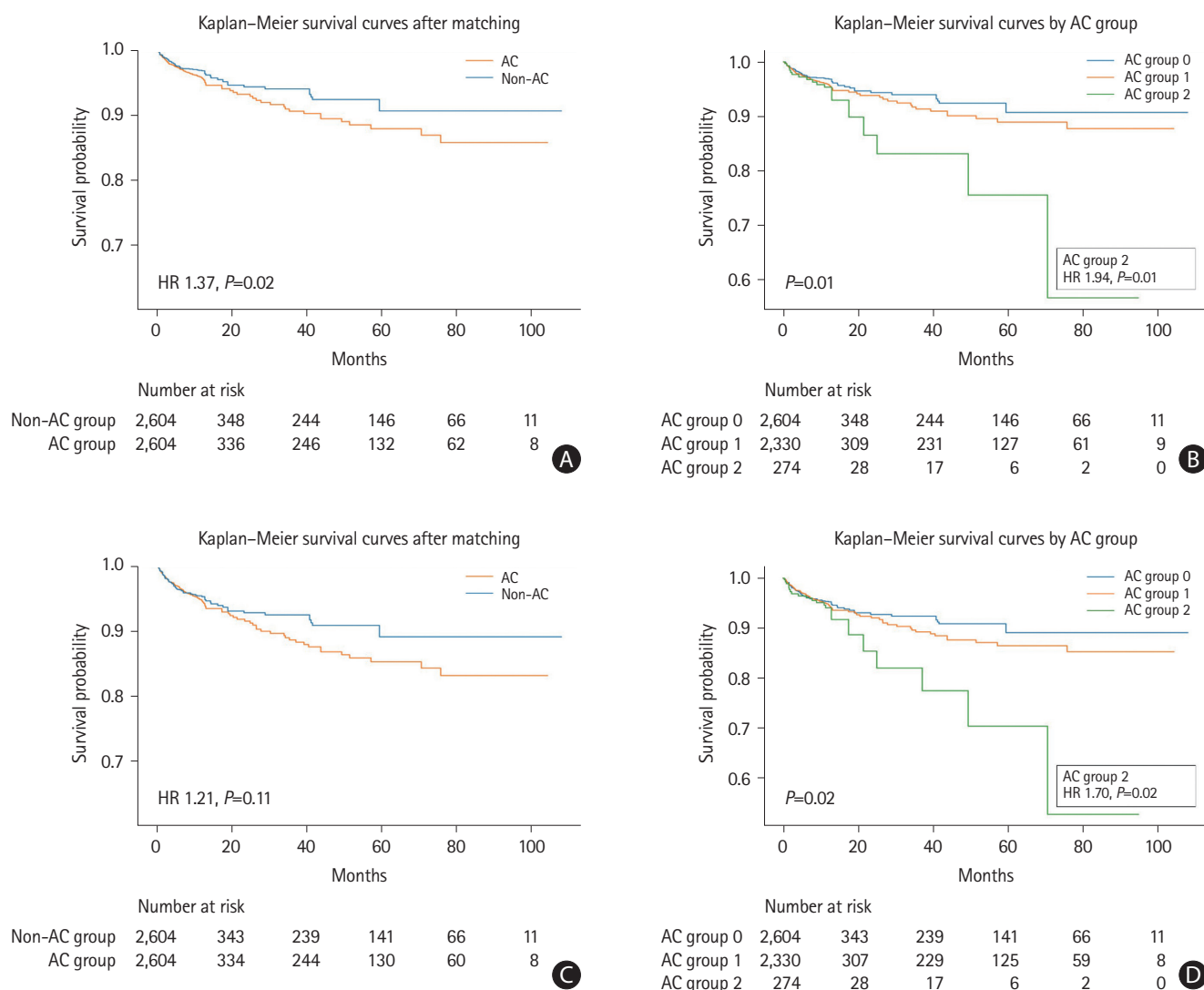


Figure 2. AC and vascular events after propensity score matching. Outcomes were compared between the AC and non-AC groups, or between the stratified groups, AC groups 0 (or the control), 1, and 2. Below the plots are the number of patients at risk (or those not yet affected by the event at a certain timepoint). The total number was 5,208 after propensity score matching. (A) The AC and the non-AC groups exhibited a difference between ischemic stroke recurrences ($P=0.02$). (B) Group 2 exhibited an increase in hazard compared to group 0 (HR 1.94, $P=0.01$). (C) The difference in MACEs was not significant due to early phase discrepancies, and (D) AC group 2 exhibited significance despite the AC and non-AC group results. AC, atrial cardiopathy; MACE, major adverse cardiovascular events; HR, hazard ratio.

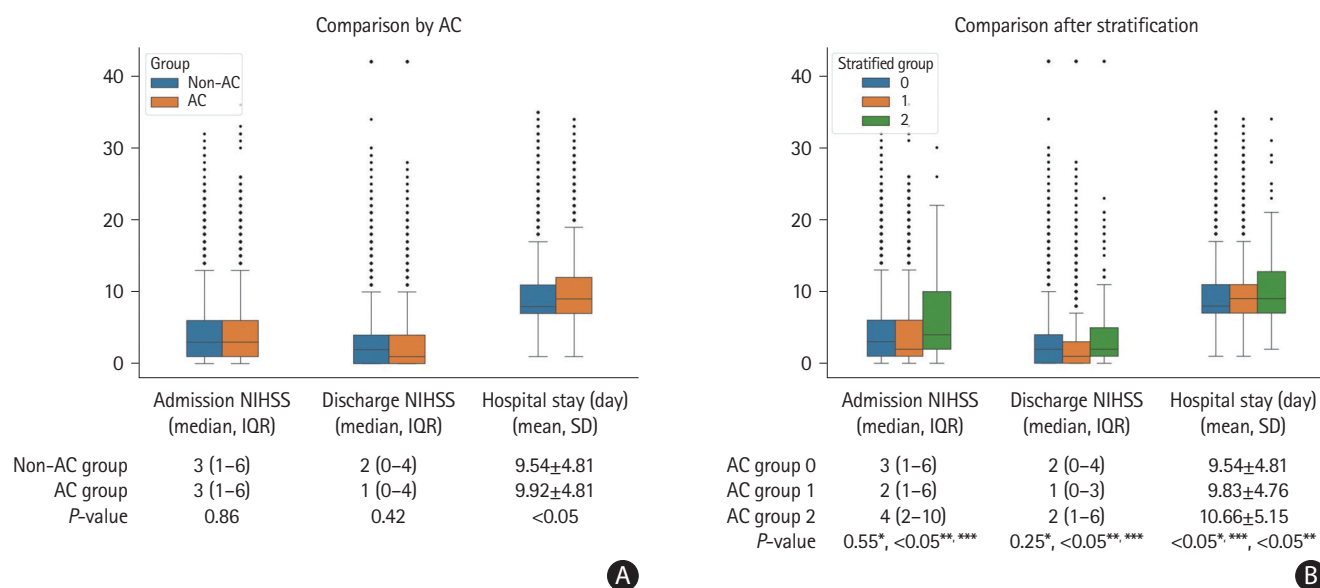


Figure 3. Stroke severity and hospitalization differences between the AC groups. Below each box plot, the median with interquartile (IQR) values or the mean with standard deviation (mean±SD) are presented, and *P*-values indicate comparison validity between the groups. Group 0 and group 1 comparison (*), group 1 and group 2 comparison (**), and group 0 and group 2 comparison (***). *P*-values are indicated in stars. (A) The Non-AC and AC groups were compared based on admission NIHSS, discharge NIHSS, and hospital stay. The former two variables did not exhibit significant differences ($P>0.05$), whereas hospital stay was significantly different ($P<0.05$). (B) Stratified groups were compared for the same variables. Groups 0 and 1 did not exhibit significant differences ($P>0.05$) for the first two variables. Group 2 exhibited significantly higher admission NIHSS scores and hospital stay duration compared to groups 0 and 1 ($P<0.05$), along with group 1 over group 0 ($P<0.05$) and group 2 over group 1 ($P<0.05$). AC, atrial cardiopathy; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; IQR, interquartile range.

those in the non-AC group by 0.29 days ($P<0.05$). Group 2 showed an increase in hospitalization by 0.83 ($P<0.05$) and 1.12 days ($P<0.05$) compared to group 1 and non-AC group, respectively (Figure 3).

Functional outcomes also supported our findings. In the entire cohort ($n=5,787$), functional decline—expressed as mRS change (discharge mRS minus admission mRS)—increased in a step-wise fashion: the median mRS change was +1 in non-AC group and group 1, and +2 in group 2 ($P<0.05$). This gradient remained after restricting the analysis to patients with baseline mRS ≤ 2 (sensitivity cohort, $n=4,913$), where median mRS change values were again +1, +1, and +2 across non-AC group, group 1, and group 2, respectively ($P<0.05$). These findings show that greater AC burden independently predicts larger in-hospital deterioration in functional status.

The effect of contributors to AC on recurrent stroke and MACE

The contributors of AC (NT-proBNP levels and the presence of LA enlargement) were assessed for their impact on the original cohort. Effects were measured for ischemic stroke recurrence using univariate Cox regression analysis, which did not exhibit significant results in both NT-proBNP levels (HR: 0.97, 95% CI: 0.84–1.12, $P=0.69$) and LA enlargement (HR: 1.15, 95% CI: 0.89–1.49, $P=0.28$) individually.

Discussion

In this large-scale multicenter study, we demonstrated the impact of AC in patients with ESUS. The multivariate results for ischemic stroke recurrence were marginal in the AC group, and the significance increased after stratification by the number of AC factors. The MACE outcomes were contradictory because neither result was significant in the AC or stratified group with two AC factors. Group 2 was associated with high NIHSS score severity, and a longer hospital stay was associated with AC. This trend was consistent across the original and PS-matched cohorts. The AC group exhibited higher significance, group 1 displayed marginal significance, and group 2 stood out. Neither NT-proBNP levels nor the presence of LA enlargement showed statistical significance.

Notably, while elevated NT-proBNP levels and LA enlargement were not strongly associated with vascular outcomes individually, their combination exhibited greater significance in ischemic stroke recurrence. This finding suggests a synergistic effect and underscores the importance of simultaneously considering multiple factors when assessing patient risk profiles.

AC as a mechanism of stroke

The concept of AC has emerged as a potential mechanism of stroke in patients with ESUS, extending beyond the traditional

markers of atrial fibrillation. This shift was supported by several key observations. Structural and functional changes in the atrial myocardium can occur before the development of detectable atrial fibrillation, creating a prothrombotic environment.^{16,17} Second, markers of atrial dysfunction such as elevated NT-proBNP levels and LA enlargement have been independently associated with stroke risk, even without documented atrial fibrillation.^{11,18} Although our study did not include electrocardiographic features, such as *P*-wave terminal force in V1 or ectopic atrial activities, they could be considered candidates for diagnosing AC. Nonetheless, our findings align with and extend previous research,^{6,19} demonstrating that the markers of atrial dysfunction collectively contribute to stroke recurrence in patients with ESUS. In contrast, MACE includes various outcomes, such as ischemic stroke, hemorrhagic stroke, and cardiac disorders, which may explain why AC was not a strong indicator of MACE in our study. However, after PS matching, group 2, despite both factors, exhibited significance, suggesting that the combination of factors contributed to the diverse vascular outcomes.

Prevalence and impact of AC in ESUS

Our study revealed that approximately 45% of patients with ESUS exhibited signs of AC, while the NAVIGATE-ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) and ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) trials reported 37% and 41%, respectively.^{3,5} Variations may emerge based on the criteria used to define atrial fibrillation. In our study, the presence of AC was associated with a 1.2–1.9 fold increase in risk of ischemic stroke recurrence, independent of other established risk factors. This association remained robust even after adjusting for potential confounders.

Previous studies have explored the relationship between various components of atrial cardiomyopathy and the recurrence of ischemic stroke. Several studies have linked LA enlargement to stroke recurrence,^{11,20,21} while others have reported an increased recurrence rate associated with elevated NT-proBNP levels.^{22,23} Additionally, other contributing factors, such as the *P*-wave terminal force in lead V1^{21,23} and the lower LA emptying fraction²⁴ have been actively investigated. Although the findings of these studies are not always consistent, a general trend indicating that these factors increase the risk of stroke recurrence has been observed. Unlike previous studies, our study demonstrated the potential utility of factor stratification in identifying patients at higher risk in a large sample. Our findings revealed a significant increase in ischemic stroke recurrence when both factors were present, compared to AC alone. This observation suggests that

the inconsistent results in previous studies may stem from varied approaches to atrial cardiomyopathy assessment, underscoring the necessity of a comprehensive evaluation of the contributing factors.

The observed increase in recurrence may be explained by several plausible explanations independent of atrial fibrillation,^{25,26} and AC itself is a predictor of covert atrial fibrillation. Different markers of AC may contribute to stroke risk through distinct but overlapping pathways. Brain natriuretic peptide has been publicized for its relevance to heart failure and atrial fibrillation, primarily due to myocardial wall stretching.^{17,27} LA dilation is also closely associated with atrial remodeling in response to multiple stressors.²⁸ A retrospective study of 32,454 community-dwelling individuals revealed that isolated LA enlargement without atrial fibrillation was a predictor of future stroke occurrence and development of atrial fibrillation.²⁹ Another possible mechanism for the increased risk of recurrent stroke is that functional and histological changes related to AC tend to cause embolic stroke. Pathological, structural, and functional changes in AC lead to aberrant blood flow and stasis in the atrial cavity, endothelial dysfunction, and hypercoagulability.³⁰ These characteristics predispose patients to thrombotic events. Ongoing research emphasizing unraveling the mechanisms underlying AC from histological to genetic perspectives, enables us to deeply associate their relevance to the current body of knowledge.^{31,32}

The tendency for severe neurological symptoms in patients with multiple AC factors is a significant finding. The severity of neurological deficits in patients with acute stroke varies according to the stroke subtype, with cardioembolic strokes often presenting more severe neurological deficits than other types.¹⁰ Therefore, the higher NIHSS scores observed in the subgroup with multiple AC factors may suggest that an undisclosed etiology in this subgroup could be cardioembolic stroke.

Limitations

Several limitations of this study must be considered when interpreting the results. First, generalizability was limited because all the subjects were Korean. Second, the retrospective design could have affected the outcome interpretation. To minimize the possibility of selection bias, PS-matching analysis was additionally employed, and the robustness increased in the PS-matched cohort. Third, the protocol for diagnosing ESUS may differ according to the participating site. The diagnosis was reviewed by a board-certified neurologist dedicated to stroke management. Fourth, the incomplete collection of AC factors hinders the precise estimation of effect sizes. The observed incompleteness may be attributable to the negative association of individual components, such as elevated NT-proBNP levels or LA enlargement,

with vascular outcomes. However, both parameters showed higher values within the AC cohort, suggesting that the analysis may have been underpowered. In clinical practice, obtaining all possible biomarkers from patients is often impractical. Furthermore, the trend of results was reproduced in a subgroup analysis of 1,739 patients, who had complete data on AC factors (Supplementary Table 2), supporting the present data. Fifth, only LA enlargement and NT-proBNP levels were used as AC factors in this study. In this study, we excluded electrophysiological factors because of the difficulty in processing and ensuring uniformity across all centers. We recognize several limitations regarding our assessment of AC. First, our definition was confined to NT-proBNP elevation and LA enlargement, excluding electrophysiological markers such as *P*-wave terminal force. Second, NT-proBNP assays were selectively requested, primarily based on clinical suspicion of heart failure or radiographic cardiomegaly, rather than following a standardized protocol, thereby reducing the generalizability of our findings. Third, a significant proportion of missing NT-proBNP and echocardiographic data likely reduced the statistical power for detecting significant associations. Nevertheless, the independent association between NT-proBNP and recurrent stroke underscores its prognostic relevance, advocating for prospective and systematic biomarker assessment to enhance study robustness in future ESUS investigations.

Conclusions

Our study demonstrates the need for AC screening in stroke patients by highlighting the association between AC and outcomes of ischemic stroke with an undetermined etiology. The strategy for identifying AC in patients with ESUS should include a comprehensive assessment encompassing various aspects of AC.

Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2025.00906>.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: WKS, SOK. Study design: WKS, SOK, SHK. Data collection: all authors. Investigation: all authors. Statistical analysis: SHK, JSL. Writing—original draft: SHK, WKS. Writing—review & editing: all authors. Funding acquisition: SOK. Approval of final manuscript: all authors.

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Supplementary Table 1. Baseline characteristics of enrolled patients

	Original cohort (n=5,787)	PS-matched cohort (n=5,208)
Age (yr)	65.90±13.88	68.62±12.73
Female sex	2,305 (39.83)	2,314 (44.43)
Body mass index (kg/m ²)	23.73±3.19	24.03±3.22
Vascular risk factors		
Peripheral arterial disease	74 (1.28)	68 (1.31)
Coronary heart disease	627 (10.83)	754 (14.48)
Hypertension	3,533 (61.05)	3,575 (68.64)
Diabetes mellitus	1,706 (29.48)	1,605 (30.82)
Dyslipidemia	2,291 (39.59)	2,085 (40.03)
Current smoker	1,545 (26.70)	1,127 (21.64)
Previous TIA	119 (2.06)	124 (2.38)
Previous stroke	1,098 (18.97)	961 (18.45)
Ischemic stroke recurrence	246 (4.25)	214 (4.11)
MACE	306 (5.29)	278 (5.34)
Admission NIHSS score	4.67±5.56	4.56±5.51
Discharge NIHSS score	3.33±5.93	3.28±5.74
Details of AC		
NT-proBNP	510±2,556 (n=1,941)	544±2,642 (n=1,811)
LAD (mm)	37.55±6.02 (n=5,092)	38.00±6.04 (n=4,590)
LAVI (mm/m ²)	33.63±14.04 (n=3,266)	34.42±14.17 (n=3,044)
Months to recurrence	16.11±19.13	15.62±18.23
Months to MACE	15.98±18.99	15.47±18.08

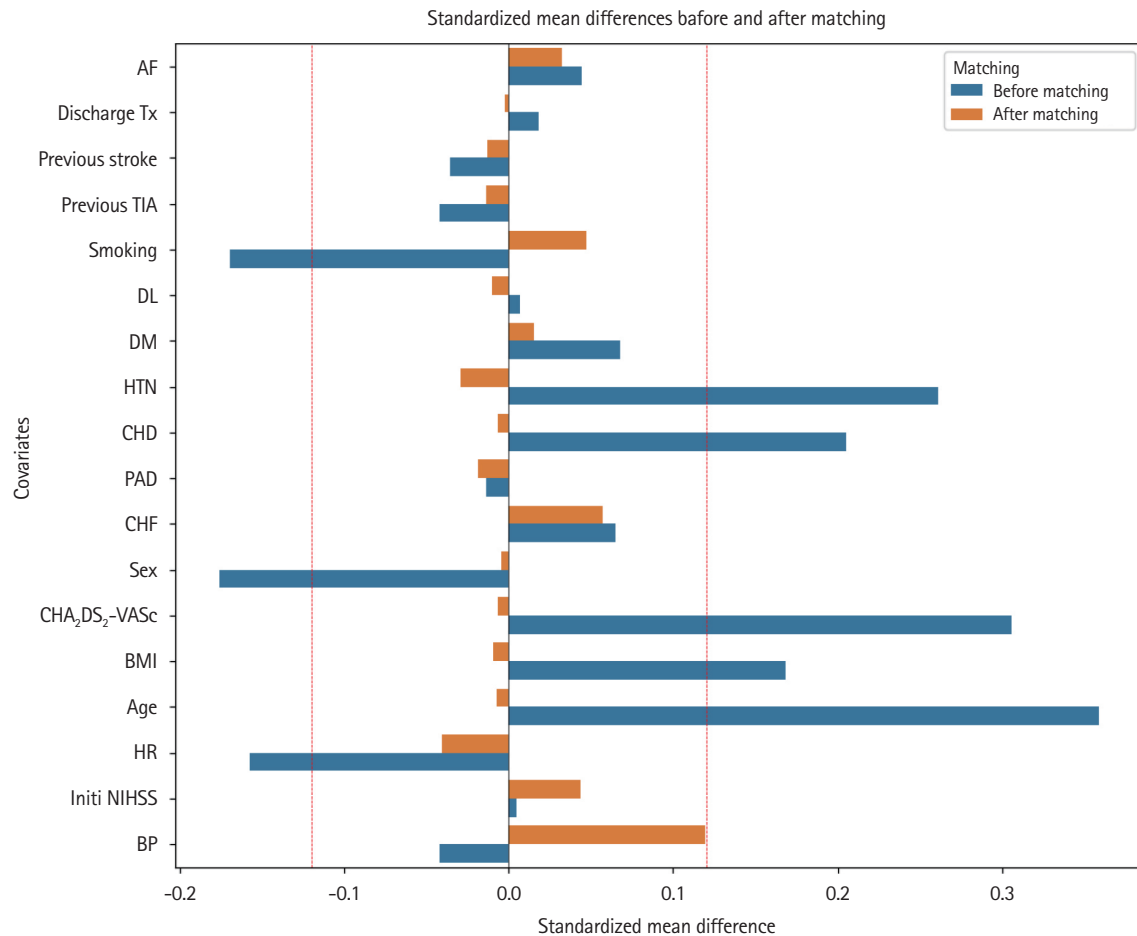
Values are presented as mena±standard deviation or n (%).

PS, propensity score; TIA, transient ischemic attack; MACE, major adverse cardiovascular event; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LAD, left atrial diameter; LAVI, left atrial volume index.

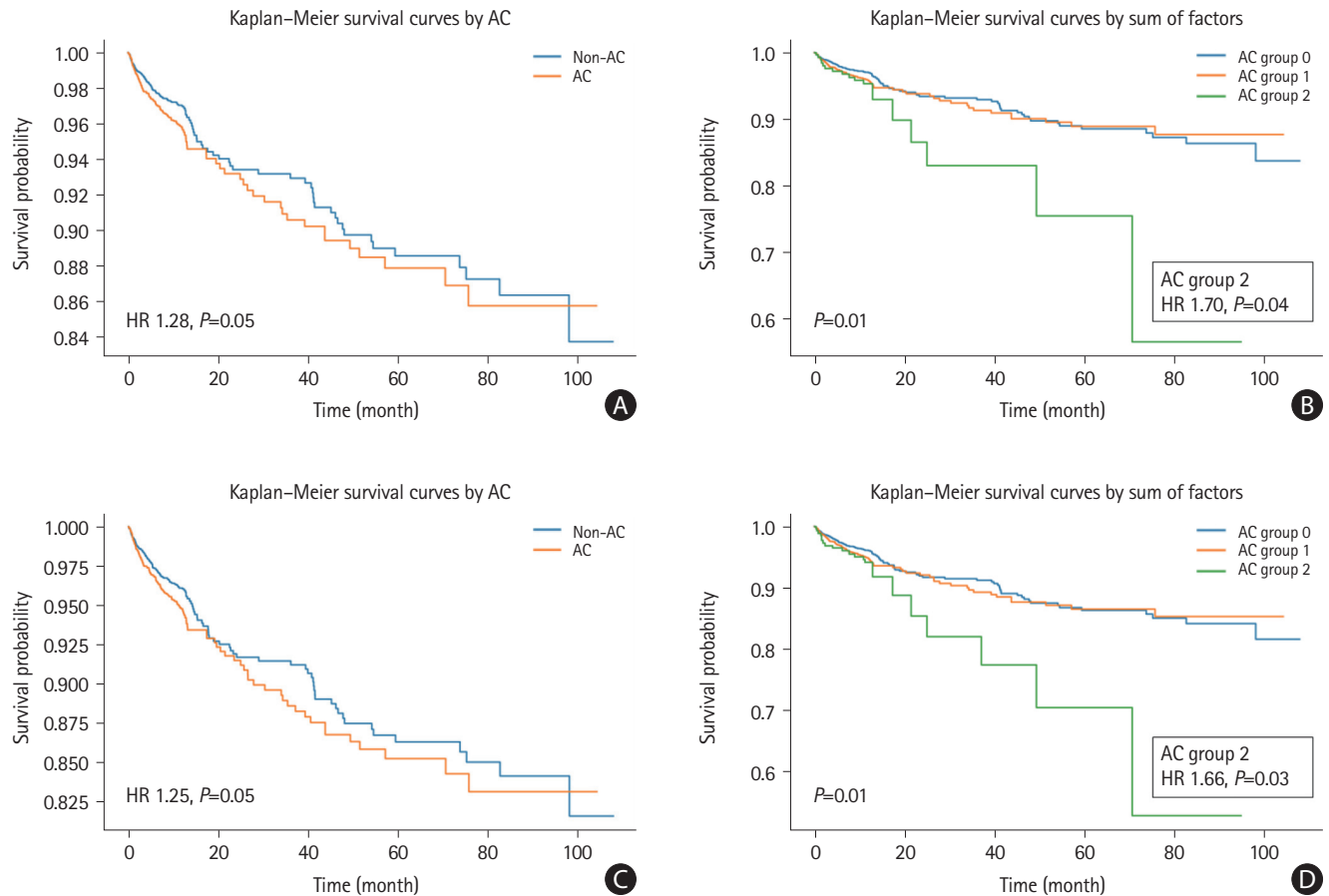
Supplementary Table 2. Effects of AC on vascular outcomes in the all-factor cohort

	All-factor cohort (n=1,739)			
	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Recurrent ischemic stroke				
Non-AC vs. AC	1.45 (0.92–2.27)	0.11	1.42 (0.91–2.23)	0.12
AC group 0	1.00 (Reference)	–	1.00 (Reference)	–
AC group 1	1.29 (0.78–2.12)	0.32	1.26 (0.77–2.08)	0.35
AC group 2	1.86 (1.03–3.34)	0.04	1.84 (1.02–3.31)	0.04
MACE				
Non-AC vs. AC	1.61 (1.05–2.45)	0.03	1.48 (0.97–2.28)	0.07
AC group 0	1.00 (Reference)	–	1.00 (Reference)	–
AC group 1	1.54 (0.98–2.43)	0.06	1.46 (0.93–2.31)	0.10
AC group 2	1.78 (1.01–3.14)	0.05	1.54 (0.85–2.77)	0.15

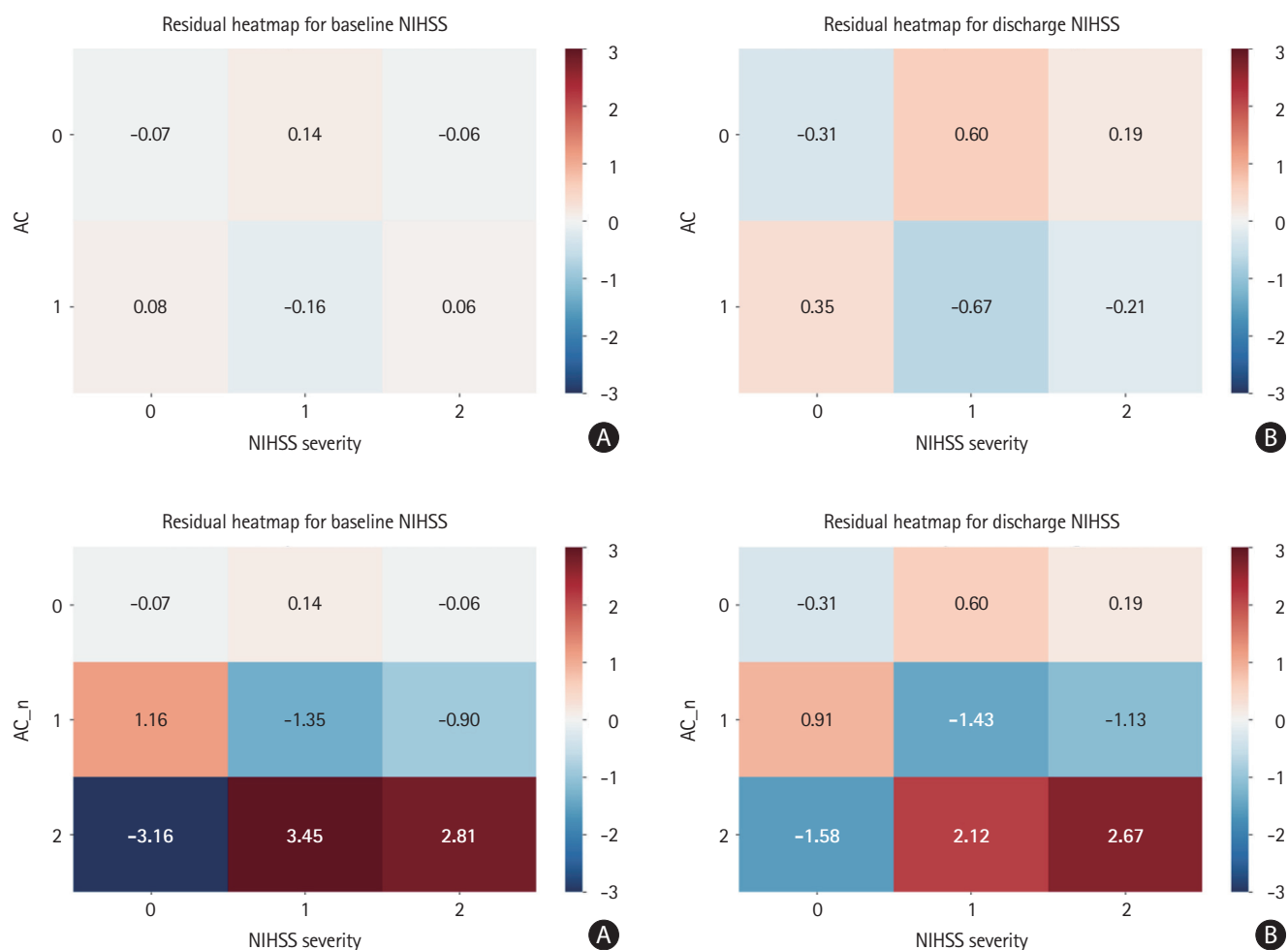
HR, hazard ratio; CI, confidence interval; AC, atrial cardiopathy; MACE, major adverse cardiovascular events.



Supplementary Figure 1. Standardized mean difference change before and after propensity score matching. Standardized mean difference change was measured before and after propensity score matching, and presented in Love plot. Red bars after matching were profoundly closer to the 0 value than blue bars before matching. The red dotted line indicates the cutoff standardized mean difference line of 0.12. AF, atrial fibrillation; TIA, transient ischemic attack; DL, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; CHD, coronary heart disease; PAD, peripheral artery disease; CHF, congestive heart failure; BMI, body mass index; HR, heart rate; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure.



Supplementary Figure 2. AC impact on vascular events within the original cohort. (A and B) The survival curves showed increase in ischemic stroke recurrence in the AC group compared to non-AC group ($P=0.05$), especially in group 2 with both risk factors ($P=0.04$). Overall significance was also confirmed when stratified ($P=0.01$). (C and D) The results were consistent in MACE results, as the AC group showed a marginal survival decrease ($P=0.05$) while group 2 displayed a larger discrepancy ($P=0.03$) after stratification (overall $P=0.01$). AC, atrial cardiopathy; MACE, major adverse cardiovascular events; HR, hazard ratio.



Supplementary Figure 3. Relevance of NIHSS severity in AC groups. NIHSS severity during admission and discharge were compared. Bars on the right side of the plots indicate correlation strength from -3 to 3. (A and B) AC did not exhibit an increase in severity during admission and discharge. (C and D) Stratified groups exhibited a greater correlation to NIHSS scores, especially group 2. AC, atrial cardiopathy; NIHSS, National Institutes of Health Stroke Scale.