

ORIGINAL RESEARCH

Artificial Intelligence–Derived Electrocardiographic Age Enhances Stroke Risk Stratification in Patients With Atrial Fibrillation With a CHA₂DS₂-VA Score of 1

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BACKGROUND: To evaluate whether artificial intelligence–derived electrocardiographic-age enhances the predictive utility of the CHA₂DS₂-VA (congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack [doubled], vascular disease, age 65–74 years) score in patients with atrial fibrillation representing a borderline indication for anticoagulation with a score of 1.

METHODS: From a multicenter atrial fibrillation and atrial flutter registry, we identified 832 anticoagulation-naïve patients with a CHA₂DS₂-VA score of 1 and at least one 12-lead ECG within 90 days of diagnosis. ECG-age was estimated using a previously validated deep learning (convolutional neural network) model. Chronological age was replaced with ECG-age (1 point for 65–74 years, 2 points for ≥75 years), leaving all other score components unchanged, to form the EA-CHA₂DS₂-VA score. Patients were grouped as EA-CHA₂DS₂-VA ≥2 (n=315) or <2 (n=517).

RESULTS: Compared with patients with an EA-CHA₂DS₂-VA score <2, those with an EA-CHA₂DS₂-VA score ≥2 had a significantly higher risk of ischemic stroke or transient ischemic attack (hazard ratio [HR], 1.82 [95% CI, 1.06–3.13]; *P*=0.028). All-cause mortality was also significantly elevated in the EA-CHA₂DS₂-VA ≥2 group (HR, 2.22 [95% CI, 1.43–3.45]; *P*<0.001). Major bleeding did not differ significantly between groups (*P*=0.386).

CONCLUSIONS: Substituting chronological age with artificial intelligence–derived ECG-age in the CHA₂DS₂-VA score was associated with improved risk stratification in patients with atrial fibrillation with intermediate stroke risk. This refined risk stratification facilitates timely initiation of anticoagulation therapy, potentially reducing stroke and mortality. Future prospective studies are essential to integrate this artificial intelligence–enhanced strategy into clinical practice.

REGISTRATION: This study was registered on the Open Science Framework (URL: <https://doi.org/10.17605/OSF.IO/39BND>; unique identifier: 10.17605/OSF.IO/39BND).

Key Words: anticoagulation ■ artificial intelligence ■ atrial fibrillation ■ CHA₂DS₂-VA score ■ ECG ■ ECG-age ■ stroke risk

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a major contributor to cardioembolic stroke worldwide.¹ Oral anticoagulation remains the cornerstone of stroke

prevention in AF²; however, its use requires careful assessment of individual thromboembolic risk and avoiding overtreatment. The CHA₂DS₂-VA (congestive heart failure/left ventricular dysfunction, hypertension,

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CLINICAL PERSPECTIVE

What Is New?

- In anticoagulation-naïve patients with atrial fibrillation with a CHA₂DS₂-VA score of 1, substituting chronological age with artificial intelligence–derived ECG-age reclassified patients into significantly higher-risk groups for ischemic stroke or transient ischemic attack (adjusted hazard ratio [HR], 1.75 [95% CI, 1.01–3.03]) and all-cause mortality (adjusted HR, 1.92 [95% CI, 1.25–3.03]).

What Are the Clinical Implications?

- Patients reclassified to an EA-CHA₂DS₂-VA score ≥ 2 had an annual stroke incidence of 2.82%, exceeding the guideline-recommended threshold for anticoagulation, without a significant increase in major bleeding risk (1.80%/year versus 1.30%/year).
- Artificial intelligence–derived ECG-age, obtainable from a standard 12-lead ECG, may offer a practical and noninvasive tool to support anticoagulation decisions in intermediate-risk patients with atrial fibrillation.

Nonstandard Abbreviations and Acronyms

AFL	atrial flutter
AI-ECG	artificial intelligence–derived ECG
CHA₂DS₂-VA	congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 years (doubled), diabetes, stroke/transient ischemic attack (doubled), vascular disease, age 65–74 years
CHA₂DS₂-VASc	congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 years (doubled), diabetes, stroke/transient ischemic attack (doubled), vascular disease, age 65–74 years, sex category
CHADS₂	congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack (doubled)
ECG-age	artificial intelligence–derived electrocardiographic age

age ≥ 75 years [doubled], diabetes, stroke/transient ischemic attack [TIA] [doubled], vascular disease, age 65–74 years) score is among the most widely validated

and guideline-endorsed tools for thromboembolic risk stratification in patients with AF, offering a simple yet validated method to quantify stroke risk based on common clinical factors.³

Despite the wide utility of the CHA₂DS₂-VA score, it has notable limitations in patients with intermediate-risk profiles. For individuals with a CHA₂DS₂-VA score of 1, the therapeutic advantage of anticoagulation has yet to be determined. In this population, the annual risk of stroke typically ranges from 1% to 2%.⁴ Clinical decisions should therefore be individualized, considering patient-specific comorbidities and treatment preferences.⁵ Among all the components in the CHA₂DS₂-VA score, age plays a particularly important role, exerting a stronger influence on cumulative stroke incidence than most other factors.⁶

Chronological age, which measures elapsed time since birth, does not fully account for the substantial interindividual variability in the pace of cardiovascular aging. Biological cardiovascular aging, by contrast, encompasses cumulative structural and electrophysiological remodeling of the heart, including atrial fibrosis, conduction system degeneration, impaired ventricular compliance, and myocardial remodeling, all of which may progress at rates markedly different from what chronological age predicts.⁷ Recent advances in artificial intelligence (AI) have enabled the estimation of “ECG-age” from standard ECGs, providing a physiological marker that captures subclinical myocardial and electrophysiological changes not reflected by chronological age alone. These changes are mechanistically relevant to thromboembolic risk in AF.^{8–10} Several studies consistently demonstrated that ECG-age is associated with increased risks of multiple comorbidities, including new-onset AF, heart failure, and mortality.^{8–11} Taken together, these findings highlight that ECG-age metrics carry important prognostic information.

However, clinical application of ECG-age in risk stratification among patients with AF has not been extensively explored. In this study, we investigated whether replacing chronological age with ECG-age in the CHA₂DS₂-VA score improves the prediction of adverse outcomes in patients with AF at intermediate stroke risk.

METHODS

Data Source and Study Population

The data that supports the findings of this study are not publicly available because of privacy and institutional restrictions but may be available from the corresponding author on reasonable request and with appropriate institutional approval. This multicenter retrospective study was approved by the Institutional Review Board of Tri-Service General Hospital, Taipei, Taiwan. The study was conducted in accordance with the Strengthening

the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.¹² Study design, data collection, statistical analyses, and reporting were performed to ensure transparency, reproducibility, and adherence to established standards for observational research. This study was conducted and reported in accordance with the European Heart Rhythm Association Artificial Intelligence Reporting Checklist for studies applying AI in cardiac electrophysiology. The completed European Heart Rhythm Association checklist is provided in the supplemental materials. Patients with AF or atrial flutter (AFL) were identified during the study period from both inpatient and outpatient department records. AF and AFL were defined using standardized diagnostic codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM codes 427.31 and 427.32), and the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM codes I48.0, I48.1, I48.2, and I48.9). The date of the first documented AF or AFL diagnosis was defined as the index date.

Patients were eligible for inclusion if they were aged ≥ 18 years, had a CHA₂DS₂-VA score of 1, and had at least one 12-lead ECG performed within 90 days of the index date. Patients with prior use of oral anticoagulants, history of valvular AF, and mechanical valve were excluded by ICD-9-CM and ICD-10-CM and medical record review. To ensure data quality, patients with missing values for CHA₂DS₂-VA score calculation or those who died within 30 days of the index date were excluded.

We retrospectively reviewed electronic medical records from January 1, 2011, to December 31, 2024. Comorbidities contributing to the CHA₂DS₂-VA score were identified using the ICD-9-CM and ICD-10-CM codes (Table S1). Baseline characteristics, including sex, age, and history of hypertension, diabetes, coronary artery disease (CAD), valvular heart disease, peripheral artery disease, or major bleeding, were also collected. All the ECGs used for ECG-age were clinically reviewed to confirm the baseline rhythm. All participants were drawn from health care institutions in Taiwan, a predominantly Han Chinese population; race and ethnicity were not recorded as study variables.

AI Model Description

We used a previously developed and validated deep learning model (AI-ECG) to estimate ECG-age.¹³ The model, an 82-layer convolutional neural network with an attention mechanism (ECG12Net), was trained on 32 707 standard 12-lead ECGs (with a further 8295 for tuning) to predict chronological age directly from the raw ECG waveform, learning physiological aging signatures rather than any single feature. Model development used health examination ECGs only, from individuals

aged 20 to 80 years and spanning all baseline rhythms, to limit the influence of acute illness. In the original validation set of 30 469 ECGs, model-estimated ECG-age correlated closely with chronological age ($r=0.822$; $R^2=66.8\%$; mean absolute error, 6.9 years), and the difference between ECG-age and chronological age was associated with incident cardiovascular disease and all-cause mortality. Detailed descriptions of the model architecture, data augmentation strategies, and performance metrics have been published previously.^{13–16} The ECG recordings used in this study were acquired using a Philips 12-lead ECG machine (PH080A) with a sampling frequency of 500 Hz and a recording duration of 10 seconds. The pretrained model was applied directly to the raw data to generate ECG-age predictions without further retraining.

ECG-Age Calculation and Risk Reclassification

For each patient, all available 12-lead ECGs obtained within a 90-day interval preceding or following the index date were analyzed using the AI-ECG model, and the mean value was calculated as the patient's baseline ECG-age to reduce reliance on any single recording obtained under a potentially unrepresentative physiological state. The CHA₂DS₂-VA score was recalculated by replacing the chronological age component with the mean baseline ECG-age, while all other components were kept unchanged. Specifically, an ECG-age of 65 to 74 years was assigned 1 point, and an ECG-age of ≥ 75 years was assigned 2 points, thereby generating the ECG-age-modified CHA₂DS₂-VA score (EA-CHA₂DS₂-VA). These cut points were intentionally kept identical to the age strata of the original CHA₂DS₂-VA score, so that the modified score preserves the guideline-endorsed structure and remains directly interpretable and comparable at the bedside; only the input variable (biological ECG-age rather than chronological age) was changed. Based on this updated score, patients were categorized into 2 groups: those with an EA-CHA₂DS₂-VA score ≥ 2 and those with an EA-CHA₂DS₂-VA score < 2 (Graphical Abstract).

Definition of Variables and Outcomes

The primary outcome was a composite of ischemic stroke or TIA. The secondary outcome was all-cause mortality and incidence of major bleeding. For stroke and TIA, time to event was defined as the period from the index date to the occurrence of an ischemic stroke or TIA, whichever came first. For mortality, survival time was defined as the period from the index date to the date of death from any cause or the last known hospital visit, whichever occurred first. Patients who initiated oral anticoagulation therapy during follow-up were censored at the date of treatment initiation. Vital status

was ascertained from electronic medical records and, where available, linked national death registry data to ensure completeness. To minimize bias from incomplete follow-up, patients who remained alive were censored at the date of their last documented hospital visit. All the outcomes were identified using standardized *ICD-9-CM* and *ICD-10-CM* codes and reviewed to confirm the accuracy.

Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria,¹⁷ fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a decrease in hemoglobin of ≥ 2 g/dL (20 g/L), or leading to a transfusion of ≥ 2 U of whole blood or red cells.

Statistical Analysis

Baseline characteristics were compared between the 2 study groups (EA-CHA₂DS₂-VA <2 versus ≥ 2). Continuous variables were assessed for normality with the Shapiro–Wilk test and for homogeneity of variance with the Levene test. As the continuous variables were nonnormally distributed, they are expressed as the median (interquartile range [IQR]) and were compared using the Mann–Whitney *U* test. Categorical variables are presented as counts and percentages and were compared using the χ^2 test or Fisher exact test, as appropriate. The primary end point of ischemic stroke or TIA and the secondary end point of all-cause mortality were analyzed using time-to-event methods. Major bleeding was evaluated using annual incidence rates, defined as the number of events per total person-years of follow-up. Cumulative incidence curves were estimated using the Kaplan–Meier method and compared between groups using the log-rank test.

To evaluate the consistency of the findings across different clinical profiles, prespecified subgroup analyses were performed stratified by age (<65 versus 65 to 75 years) and sex. Survival outcomes among these groups were compared using Kaplan–Meier analysis and Cox regression models. To determine the independent prognostic value of the EA-CHA₂DS₂-VA score, hazard ratios (HRs) and 95% CIs were calculated using multivariable Cox proportional hazards regression models. Covariates were selected a priori on clinical grounds: age and sex are constituent components of the CHA₂DS₂-VA score, and heart failure and CAD are established risk factors for stroke and mortality in AF. To avoid overfitting given the number of events, adjustment was restricted to these clinically prespecified covariates that also differed significantly between groups at baseline (age, heart failure, and CAD), rather than using automated stepwise selection.

To address the potential bias introduced by the competing risk of death, we used the Fine and Gray proportional subdistribution hazards regression model. We estimated subdistribution HRs with 95% CIs. Cumulative incidence functions for ischemic stroke/TIA were additionally estimated treating all-cause mortality as a competing event, with between-group differences assessed using the Gray test. The proportional hazards assumption for the Cox models and the proportional subdistribution hazards assumption for the Fine and Gray models were verified using Schoenfeld residuals. To account for oral anticoagulant initiation during follow-up, a time-varying Cox regression model was applied, in which oral anticoagulant use was treated as a time-dependent covariate. Propensity score–based inverse probability of treatment weighting was used to balance baseline covariates between EA-CHA₂DS₂-VA groups. Stabilized weights were truncated at the 1st and 99th percentiles, and weighted Cox proportional hazards models were fitted. Covariate balance before and after weighting was assessed using standardized mean differences, with values <0.2 indicating adequate balance. Additional sensitivity analyses were also performed: landmark analyses with blanking periods of 30, 60, and 90 days and the earliest ECG time; exclusion of patients whose CHA₂DS₂-VA score progression was attributable solely to chronological aging during follow-up; exclusion of patients with AFL; and analyses restricted to patients whose baseline ECGs were sinus rhythm, AF, and AFL. Each sensitivity analysis was prespecified to address a specific threat to validity: exclusion of patients with AFL, because the CHA₂DS₂-VA score was validated primarily in nonvalvular AF; landmark analyses, to address immortal-time and reverse-causation concerns; exclusion of patients whose score increased solely through chronological aging, to address residual confounding by chronological age; restriction by baseline rhythm, because ECG-age estimation is rhythm dependent; inverse probability of treatment weighting, to address residual baseline confounding; and the time-varying model, to account for oral anticoagulant initiation during follow-up.

All statistical analyses were performed using R software, version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P*<0.05 was considered statistically significant.

RESULTS

Study Population

A total of 38 443 patients with AF or AFL were identified during the study period from the multicenter registry, including 14 740 from a medical center (Tri-Service General Hospital), 18 590 from 4 regional hospitals, and 5113 from 2 district hospitals. After applying the

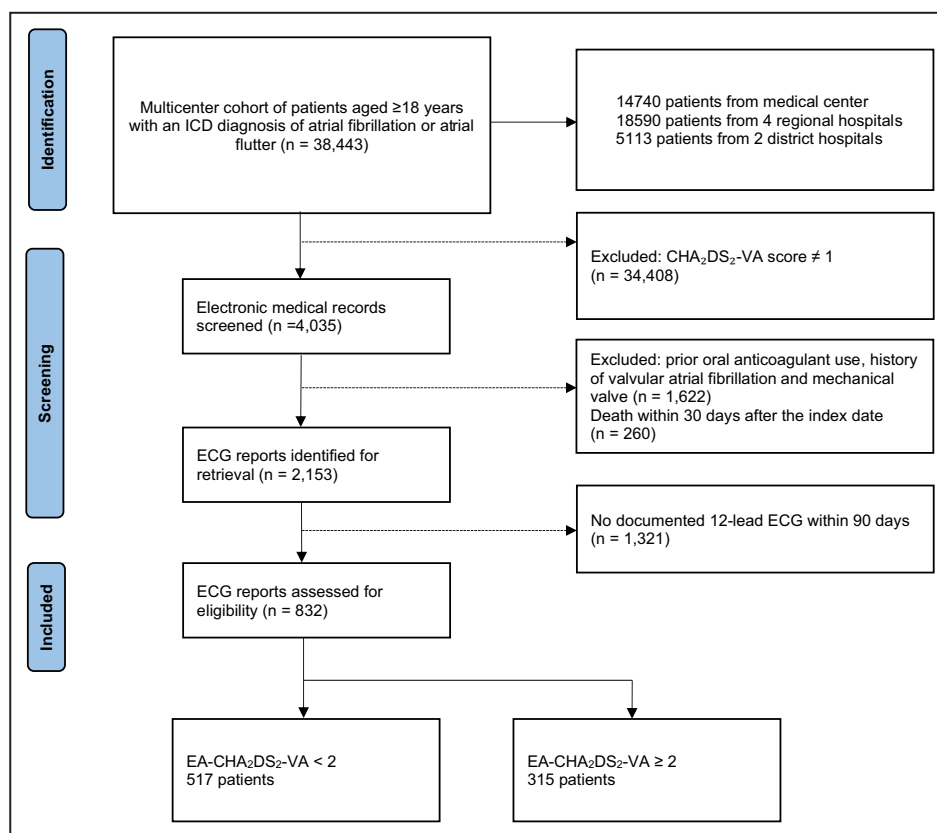


Figure 1. Flowchart of patient selection and study inclusion.

Adult patients (aged ≥ 18 years) with an ICD diagnosis of atrial fibrillation or atrial flutter were identified from a multicenter electronic medical record database, including 1 medical center, 4 regional hospitals, and 2 district hospitals. Patients with a CHA₂DS₂-VA score other than 1 were excluded. After ECG report retrieval, patients were further excluded for prior oral anticoagulant use, death within 30 days after the index date, or absence of a documented 12-lead ECG within 90 days of the index date. The final study cohort was stratified according to the EA-CHA₂DS₂-VA into < 2 and ≥ 2 groups. CHA₂DS₂-VA indicates congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 years (doubled), diabetes, stroke/transient ischemic attack (doubled), vascular disease, age 65–74 years; EA-CHA₂DS₂-VA, ECG-age-modified CHA₂DS₂-VA; and ICD, *International Classification of Diseases*.

inclusion and exclusion criteria, 832 patients with a CHA₂DS₂-VA score of 1 were included in the final analysis. The mean number of ECGs per patient used for ECG-age calculation was 2.48 ± 2.62 , with a median of 2 (IQR, 1–3). The distribution of baseline ECG rhythm was summarized in Figure S1. Based on the ECG-age-modified score, 517 patients (62.1%) had an EA-CHA₂DS₂-VA score < 2 , whereas 315 patients (37.9%) had an EA-CHA₂DS₂-VA score ≥ 2 (Figure 1).

Baseline characteristics are summarized in Table 1. Compared with patients with an EA-CHA₂DS₂-VA score < 2 , those with an EA-CHA₂DS₂-VA score ≥ 2 were older (median, 63.1 [IQR, 57.7–68.9] versus 61.9 [IQR, 53.0–67.8] years; $P=0.002$) and had substantially higher ECG-age (75.6 [IQR, 70.0–78.8] versus 59.1 [IQR, 52.1–64.6] years; $P<0.001$). They also had a higher prevalence of heart failure (7.9% versus 4.1%; $P=0.023$), whereas CAD was more common among

patients with an EA-CHA₂DS₂-VA score < 2 (22.9% versus 15.5%; $P=0.013$). In the EA-CHA₂DS₂-VA ≥ 2 group, AF subtypes comprised 2.5% AFL, 56.8% paroxysmal AF, and 40.6% persistent AF, whereas in the EA-CHA₂DS₂-VA < 2 group, the corresponding proportions were 3.7%, 59.1%, and 37.1%, respectively. The median time to event for ischemic stroke and TIA was 1.4 (IQR, 0.4–3.7) years in the EA-CHA₂DS₂-VA score ≥ 2 group and 2.1 (IQR, 0.8–7.1) years in the EA-CHA₂DS₂-VA < 2 group, while the corresponding period for all-cause mortality was 2.2 (IQR, 1.0–7.2) years and 3.7 (IQR, 1.4–8.9) years, respectively.

Clinical Outcomes

During follow-up, patients with an EA-CHA₂DS₂-VA score ≥ 2 demonstrated significantly higher risks of ischemic stroke or TIA and all-cause mortality compared

Table 1. Baseline Characteristics of Patients Stratified by EA-CHA₂DS₂-VA Score

Variable	EA-CHA ₂ DS ₂ -VA ≥2 (n=315)	EA-CHA ₂ DS ₂ -VA <2 (n=517)	P value
Sex			0.160
Female	118 (37.5)	169 (32.7)	
Male	197 (62.5)	348 (67.3)	
Age, y	63.1 (57.7 to 68.9)	61.9 (53.0 to 67.8)	0.002
Cardiac age	75.6 (70.0 to 78.8)	59.1 (52.1 to 64.6)	
Delta age	11.7 (7.8 to 15.6)	−1.3 (−5.7 to 3.4)	
Height (cm)	165.0 (158.0 to 172.0)	168.0 (162.0 to 173.0)	0.016
Weight (kg)	66.0 (58.0 to 81.8)	68.0 (59.7 to 76.4)	0.70
Heart failure	23 (7.9)	20 (4.1)	0.023
Type 2 diabetes	25 (8.6)	31 (6.3)	0.233
Coronary artery disease	45 (15.5)	112 (22.9)	0.013
Hypertension	90 (31.0)	143 (29.2)	0.598
Peripheral artery disease	2 (0.7)	6 (1.2)	0.717#
Valvular heart disease	42 (14.5)	75 (15.3)	0.747
Major bleeding	16 (5.1)	28 (5.4)	0.833
Antiplatelet therapy	61 (19.4)	106 (20.5)	0.691
EA-CHA ₂ DS ₂ -VA			
EA-CHA ₂ DS ₂ -VA=0	0 (0.0)	75 (14.5)	
EA-CHA ₂ DS ₂ -VA=1	0 (0.0)	442 (85.5)	
EA-CHA ₂ DS ₂ -VA=2	261 (82.9)	0 (0.0)	
EA-CHA ₂ DS ₂ -VA=3	54 (17.1)	0 (0.0)	
Stroke follow-up time (y)	1.4 (0.4 to 3.7)	2.1 (0.8 to 7.1)	
Mortality follow-up time (y)	2.2 (1.0 to 7.2)	3.7 (1.4 to 8.9)	

Data are median (25th to 75th percentile) for continuous variables and number (percentage) for categorical variables. Continuous variables were compared using the Mann–Whitney *U* test; categorical variables using the Pearson χ^2 test or Fisher exact test when any expected cell count was <5 (denoted number). Normality and homogeneity of variance were assessed with the Shapiro–Wilk and Levene tests, respectively. EA-CHA₂DS₂-VA indicates artificial intelligence–derived electrocardiographic age–modified CHA₂DS₂-VA (congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack [doubled], vascular disease, age 65–74 years).

with those with an EA-CHA₂DS₂-VA score <2. As shown in [Figure 2](#), Kaplan–Meier analysis demonstrated a higher cumulative incidence of ischemic stroke or TIA in patients with an EA-CHA₂DS₂-VA score ≥2 (log-rank *P*=0.016). Consistently, the cumulative incidence of all-cause mortality was also significantly higher in group of EA-CHA₂DS₂-VA score ≥2, as presented in [Figure S2](#). In unadjusted Cox analyses, patients with an EA-CHA₂DS₂-VA score ≥2 had a significantly higher risk of ischemic stroke or TIA compared with those with a score <2 (hazard ratio [HR], 1.82 [95% CI, 1.06–3.13]; *P*=0.028). This association remained significant after adjustment for age and sex, as well as heart failure and CAD, which were the only baseline characteristics that differed significantly between the 2 groups (HR, 1.75 [95% CI, 1.01–3.03]; *P*=0.045). For all-cause mortality, unadjusted analyses showed that patients with an EA-CHA₂DS₂-VA score ≥2 had more than twice the risk compared with those with a score <2 (HR, 2.22 [95% CI, 1.43–3.45]; *P*<0.001), and the association persisted after adjustment for age and sex, as well as heart failure and CAD (HR, 1.92 [95% CI, 1.25–3.03]; *P*=0.003) ([Table 2](#)).

Patients with an EA-CHA₂DS₂-VA score ≥2 had a significantly higher annual incidence of ischemic stroke or TIA, as well as all-cause mortality, compared with those with a score <2 (2.82%/year versus 1.48%/year; *P*=0.017). In contrast, the annual incidence of major bleeding was only slightly higher in patients with an EA-CHA₂DS₂-VA score ≥2 (1.80%/year versus 1.30%/year), and this difference did not reach statistical significance (*P*=0.386) ([Table S2](#), [Figure S3](#)).

Subgroup Analyses

Subgroup analyses stratified by age demonstrated notable differences in ischemic stroke or TIA and all-cause mortality between patients with an EA-CHA₂DS₂-VA score ≥2 and those with a score <2 ([Figure 3](#)). Among patients aged <65 years, those with an EA-CHA₂DS₂-VA score ≥2 had a significantly higher cumulative incidence of ischemic stroke or TIA compared with patients with a score <2 (*P*=0.003), whereas no significant difference was observed in the age 65-to-75-year subgroup (*P*=0.60). A similar age-specific pattern was observed for all-cause mortality ([Figure S4](#)).

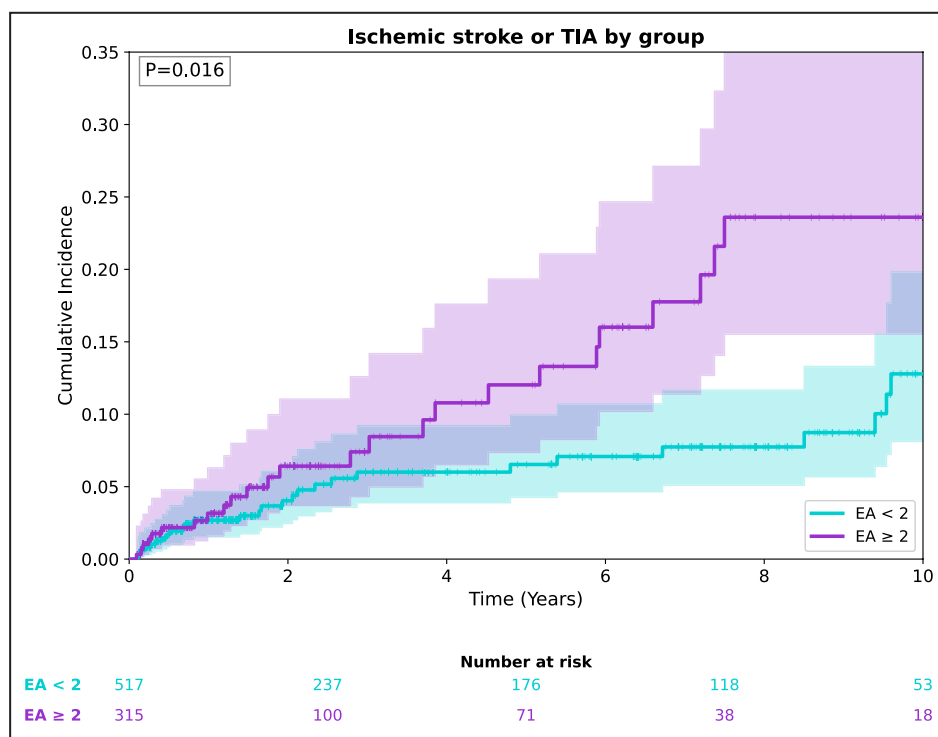


Figure 2. Cumulative incidence of ischemic stroke or TIA stratified by EA-CHA₂DS₂-VA score.

Kaplan-Meier curves comparing the cumulative incidence of ischemic stroke or TIA between patients with EA-CHA₂DS₂-VA <2 and EA-CHA₂DS₂-VA ≥2 over a 10-year follow-up. Patients in the EA-CHA₂DS₂-VA ≥2 group exhibited a significantly higher event rate (log-rank $P=0.016$). Number-at-risk tables are presented below the plot. EA-CHA₂DS₂-VA indicates ECG-age-modified CHA₂DS₂-VA (congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack [doubled], vascular disease, age 65–74 years); and TIA, transient ischemic attack.

Sex-stratified analyses showed consistent findings across sexes, with patients with an EA-CHA₂DS₂-VA score ≥2 exhibiting higher rates of ischemic stroke or TIA and all-cause mortality compared with those with a score <2 (Figure 4). For ischemic stroke or TIA, patients with an EA-CHA₂DS₂-VA score ≥2 had a higher

cumulative incidence in both women and men; however, statistical significance was reached only in men ($P=0.033$), whereas women demonstrated a nonsignificant trend toward higher stroke incidence (log-rank $P=0.21$). For all-cause mortality, patients with an EA-CHA₂DS₂-VA score ≥2 had significantly higher mortality

Table 2. Cox Proportional Hazards Models for Ischemic Stroke/TIA and All-Cause Mortality

Outcome	Model	Variable	No. (events)	HR (95% CI)	P value
Ischemic stroke or TIA	Crude	EA-CHA ₂ DS ₂ -VA <2	517 (30)	Reference	...
		EA-CHA ₂ DS ₂ -VA ≥2	315 (25)	1.82 (1.06–3.13)	0.028
	Adjusted*	EA-CHA ₂ DS ₂ -VA <2		Reference	...
		EA-CHA ₂ DS ₂ -VA ≥2		1.75 (1.01–3.03)	0.045
All-cause mortality	Crude	EA-CHA ₂ DS ₂ -VA <2	517 (39)	Reference	...
		EA-CHA ₂ DS ₂ -VA ≥2	315 (43)	2.22 (1.43–3.45)	<0.001
	Adjusted*	EA-CHA ₂ DS ₂ -VA <2		Reference	...
		EA-CHA ₂ DS ₂ -VA ≥2		1.94 (1.25–3.01)	0.003

All P values are statistically significant ($P<0.05$). EA-CHA₂DS₂-VA indicates artificial intelligence–derived electrocardiographic age–modified CHA₂DS₂-VA (congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack [doubled], vascular disease, age 65–74 years); HR, hazard ratio; and TIA, transient ischemic attack.

*Adjusted for age, heart failure, and coronary artery disease.

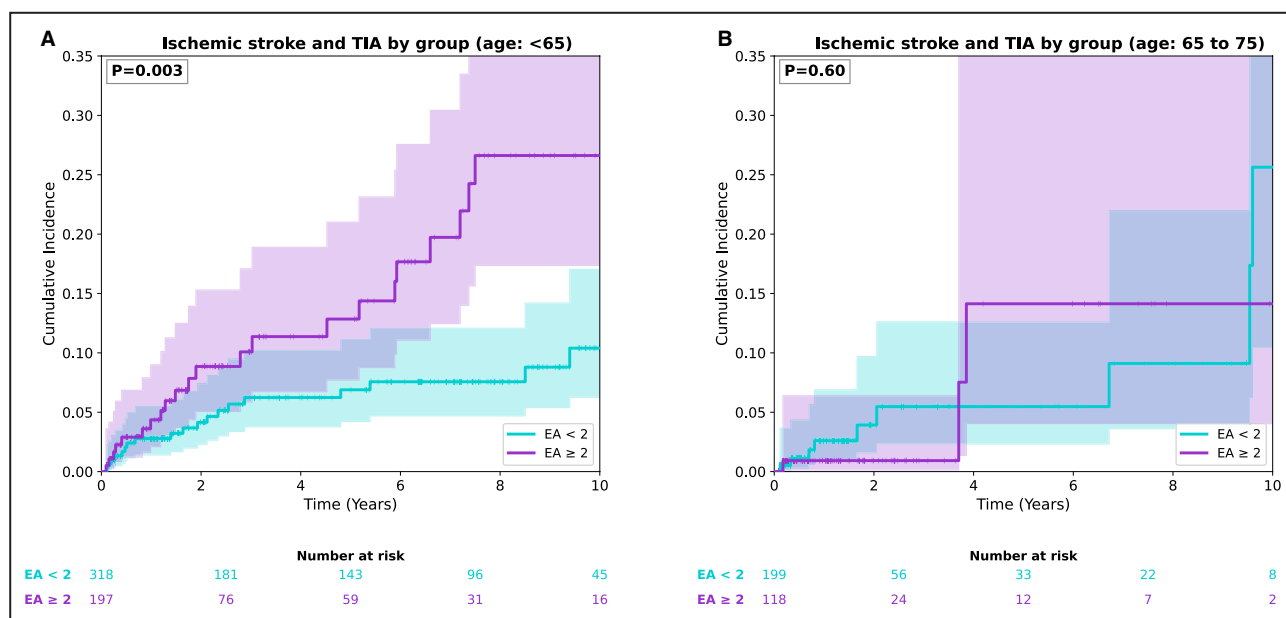


Figure 3. Subgroup analysis: cumulative incidence of ischemic stroke or TIA stratified by age.

A, Ischemic stroke or TIA in patients aged <65 years, showing a significantly higher cumulative incidence in the EA-CHA₂DS₂-VA ≥2 group (log-rank $P=0.003$). **B**, Ischemic stroke or TIA in patients aged from 65 to 75 years, showing no significant difference between groups (log-rank $P=0.60$). EA-CHA₂DS₂-VA indicates ECG-age-modified CHA₂DS₂-VA (congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack [doubled], vascular disease, age 65–74 years); and TIA, transient ischemic attack.

in both female ($P=0.004$) and male ($P=0.019$) subgroups (Figure S5). In subgroup analyses based on individual EA-CHA₂DS₂-VA reclassification, higher reclassified

scores were associated with progressively higher risks of stroke and mortality, with particularly elevated mortality among patients upgraded to a score of 3 (Table S3).

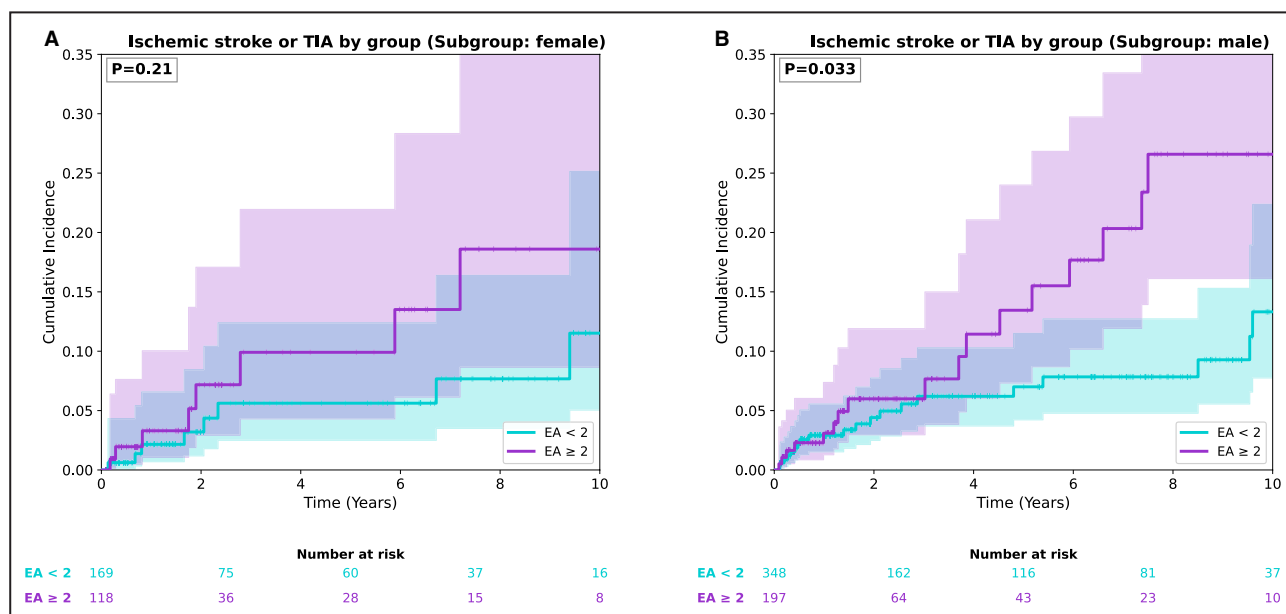


Figure 4. Subgroup analysis by sex: cumulative incidence of ischemic stroke or TIA.

A, Ischemic stroke or TIA in female patients, showing a nonsignificant trend toward higher event rates in the EA-CHA₂DS₂-VA ≥2 group (log-rank $P=0.21$). **B**, Ischemic stroke or TIA in male patients, showing significantly higher risk in the EA-CHA₂DS₂-VA ≥2 group (log-rank $P=0.033$). EA-CHA₂DS₂-VA indicates ECG-age-modified CHA₂DS₂-VA (congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack [doubled], vascular disease, age 65–74 years); and TIA, transient ischemic attack.

Sensitivity Analyses

To address potential confounding from CHA₂DS₂-VA score progression attributable to age-related point increases, we performed sensitivity analyses excluding patients whose score increase during follow-up solely because of chronological aging. Even after this exclusion, patients with an EA-CHA₂DS₂-VA score ≥ 2 continued to have significantly higher risks of ischemic stroke or TIA ($P=0.004$) and all-cause mortality ($P=0.003$; Figure S6).

Using unadjusted Cox proportional hazards models, patients with an EA-CHA₂DS₂-VA score ≥ 2 showed a significantly higher risk of ischemic stroke or TIA compared with those with a score < 2 (HR, 1.82 [95% CI, 1.06–3.13]; $P=0.028$). When mortality was treated as a competing event, the Fine–Gray subdistribution hazard model produced similar results, demonstrating a significantly increased stroke risk in patients with an EA-CHA₂DS₂-VA score ≥ 2 (subdistribution HR, 1.75 [95% CI, 1.02–3.01]; $P=0.043$). The concordance of findings was found across both Cox and Fine–Gray models (Figure S7). Cumulative incidence functions estimated with death as a competing event were concordant with the Fine–Gray model estimates (Figure S8). After inverse probability of treatment weighting, baseline covariates were well balanced. EA-CHA₂DS₂-VA ≥ 2 was associated with increased risks of ischemic stroke or TIA (HR, 1.85 [95% CI, 1.08–3.18]; $P=0.025$) and all-cause mortality (HR, 2.02 [95% CI, 1.31–3.13]; $P=0.002$) (Figures S4 and S9).

In time-varying Cox models incorporating oral anticoagulant use as a time-dependent covariate, EA-CHA₂DS₂-VA ≥ 2 remained significantly associated with higher risks of ischemic stroke/TIA (HR, 1.74 [95% CI, 1.02–2.98]; $P=0.041$) and all-cause mortality (HR, 2.11 [95% CI, 1.37–3.27]; $P<0.001$), with only minimal attenuation compared with the primary analysis (Figure S10).

A prespecified sensitivity analysis excluding the 27 patients with AFL (3.2% of the total cohort) yielded results fully consistent with the primary analysis. Among the remaining 805 patients with AF only, EA-CHA₂DS₂-VA ≥ 2 remained associated with significantly higher cumulative incidence of ischemic stroke/TIA ($P=0.02$) and all-cause mortality (Figure S11), confirming that the primary findings were not attributable to AFL inclusion. Prespecified landmark analyses using blanking periods of 30, 60, and 90 days, and the time of the earliest ECG as the landmark, showed consistent results across all analyses (Figure S12). A sensitivity analysis restricted to patients with baseline rhythm of sinus rhythm, AF, and AFL, excluding those using any one of other rhythm for ECG-age calculation, yielded similar results (Figure S13). Among patients in sinus rhythm at baseline ($n=373$), ECG-age reclassification remained significantly associated with all-cause mortality (HR, 3.52 [95% CI, 1.77–6.98]; $P<0.001$) and showed a directionally consistent but statistically nonsignificant

association with ischemic stroke/TIA (HR, 1.88 [95% CI, 0.77–4.57]), likely owing to limited statistical power in this subgroup (Figure S14). In an exploratory analysis, ECG-age as a continuous variable was independently associated with both ischemic stroke and TIA and all-cause mortality, irrespective of its incorporation into the CHA₂DS₂-VA framework (Figure S15). Restricted cubic spline modeling confirmed a monotonic dose–response relationship between ECG-age and all-cause mortality without significant nonlinearity, and a positive although less precise association with ischemic stroke or TIA (Figure S16).

DISCUSSION

In this multicenter study of patients with AF and AFL with intermediate stroke risk, replacing chronological age with ECG-age in the CHA₂DS₂-VA score was associated with risk stratification that identified patients at significantly higher risk of ischemic stroke or TIA and all-cause mortality. After reclassification, patients with an EA-CHA₂DS₂-VA score ≥ 2 had an annual stroke incident rate of 2.82%, whereas patients with an EA-CHA₂DS₂-VA score < 2 remained at 1.48%. Baseline major bleeding risk was comparable between groups before initiation of anticoagulation. All-cause mortality was similarly stratified by EA-CHA₂DS₂-VA category. These findings suggest that integrating ECG-age may help identify a higher-risk subgroup within the CHA₂DS₂-VA=1 population, supporting more precise risk stratification and clinical decision-making.

Anticoagulant therapy in AF is primarily intended to prevent ischemic stroke and systemic embolism, yet these benefits must be weighed against the risk of bleeding. Notably, most pivotal trials enrolled patients with an estimated baseline stroke risk of $\approx 2\%$ per year (eg, a CHADS₂ [Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke/transient ischemic attack (doubled)] score ≥ 2),^{18–21} effectively using this as a treatment threshold. A Markov state-transition decision model demonstrated that anticoagulation becomes the favored strategy once the annual stroke risk surpasses $\approx 1.7\%$.²² These observations support the use of a threshold of $\approx 2\%$ per year for stroke or systemic embolism, beyond which the anticipated clinical benefit of anticoagulation clearly outweighs its bleeding risk. Furthermore, because oral anticoagulation confers a broadly consistent relative risk reduction across different risk strata, patients with higher baseline stroke risk derive a proportionally greater absolute reduction in stroke events.^{2,5,22}

Individuals with EA-CHA₂DS₂-VA ≥ 2 had an annual stroke incidence of 2.82%, exceeding the treatment threshold recommended by current guidelines, which generally support anticoagulation when the annual stroke risk surpasses 2%.²³ In contrast, those

EA-CHA₂DS₂-VA <2 had a lower incidence of 1.48% per year. In the absence of a definitive risk-prediction model for intermediate-risk AF, guidelines advocate for a more nuanced approach integrating shared decision-making with high-risk comorbidity assessment.⁵ Our study reinforces this recommendation. These findings suggest that EA-CHA₂DS₂-VA may help identify a higher-risk subgroup within the CHA₂DS₂-VA=1 population; however, the 2% annual stroke risk threshold referenced here is derived from prior models based on the CHADS₂ score and is cited for contextual reference only. Whether this threshold should inform anticoagulation decisions in EA-CHA₂DS₂-VA-stratified patients requires prospective validation.

Evidence from the Norwegian AFNOR (Atrial Fibrillation in Norway) study²⁴ further shows that the bleeding risk associated with anticoagulation in patients with a CHA₂DS₂-VA score of 1 is minimal, with major bleeding increasing only slightly from 1.14% to 1.33% per year. Although our study did not include data on anticoagulant use, the consistency between our observed stroke and bleeding rates and those reported in real-world cohorts suggests that ECG-age identified high-risk individuals may derive similar benefit from anticoagulation, with the potential stroke prevention outweighing the incremental bleeding risk. However, the present study cannot establish whether anticoagulation in patients reclassified to EA-CHA₂DS₂-VA ≥2 would confer net clinical benefit; the observed risk elevation is hypothesis generating and warrants evaluation in prospective, ideally randomized, studies.

Previous studies have demonstrated that the CHA₂DS₂-VASc (Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, Stroke/transient ischemic attack [doubled], Vascular disease, Age 65–74 years, and Sex category) score predicts mortality in patients both with and without AF, and independent of anticoagulation status.^{25,26} Our study yielded consistent findings. Patients with an EA-CHA₂DS₂-VA ≥2 had significantly higher mortality than those with EA-CHA₂DS₂-VA <2. These results indicate that ECG-age is a meaningful predictor of mortality in the same way as the traditional CHA₂DS₂-VASc score.

Heart failure was substantially more common in patients with EA-CHA₂DS₂-VA ≥2, consistent with the strong impact of diffuse ventricular and atrial remodeling on ECG-derived aging signatures.⁸ However, in our study, CAD showed a negative association with having an EA-CHA₂DS₂-VA ≥2. This likely reflects the characteristics of our cohort, in which patients had AF and only 1 comorbidity. All CAD cases in our cohort were probably stable or nonobstructive and not accompanied by additional risk factors. Importantly, after inverse probability of treatment weighting, baseline covariates were well balanced between groups, suggesting that the observed associations were not driven by residual confounding.

In the subgroup analysis by age, there was no significant difference in the 65- to 75-year subgroup. This finding is likely attributable to the fact that these patients had no comorbidities other than age itself. In this unique population, chronological age serves as the dominant determinant of stroke risk, leaving limited scope for ECG-age to provide additional discriminative value. As a result, the incremental contribution of ECG-age becomes markedly attenuated in this older but comorbidity-free subgroup.

There are still some limitations in this study. First, the retrospective design and reliance on ICD-9-CM and ICD-10-CM coded data introduce potential misclassification bias and may limit generalizability. In addition, the relatively small number of eligible patients remains a limitation. Second, although the use of mean ECG-age across multiple recordings and rhythm-restricted sensitivity analyses were used to reduce the influence of acute physiological states, ECG-age estimated under acute clinical conditions may itself carry distinct prognostic significance reflecting acute physiological burden. Whether ECG-age obtained during acute presentations differs meaningfully from that obtained under stable conditions, and its implications for risk stratification, remain important and warrant future prospective investigation. Third, although data were collected from a multicenter network in Taiwan, external validation in independent, geographically and ethnically diverse cohorts has not been performed, and generalizability to other populations remains uncertain. Finally, the evaluation of anticoagulant use was inherently limited because of retrospective design being subject to substantial confounding, and future prospective studies in larger multicenter cohorts are warranted.

In summary, incorporating ECG-age into the CHA₂DS₂-VA score was associated with improved risk discrimination in patients with AF with intermediate stroke risk. ECG-age reflects biological aging processes not captured by chronological age and helps identify patients with concealed stroke risk. Because ECG-age is derived noninvasively from a standard 12-lead ECG, it offers a practical and scalable tool to support clearer anticoagulation decisions.

CONCLUSIONS

In this study, we demonstrated that the EA-CHA₂DS₂-VA score enhanced the risk stratification of stroke in intermediate-risk population with AF with CHA₂DS₂-VA of 1. Patients with EA-CHA₂DS₂-VA ≥2 had significantly higher risks of ischemic stroke or TIA and all-cause mortality. The AI-derived ECG-age offers a rapid, noninvasive, and scalable tool to support clinical decision of anticoagulation in clinical practice.

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Supplemental Material

Tables S1–S4
Figures S1–S16
EHRA Checklist
STROBE Checklist

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