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Novel electrocardiographic classification for stroke prediction in atrial fibrillation patients undergoing cardioversion

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ABSTRACT

BACKGROUND Abnormal conduction, structure, and function of the atrial myocardium predispose to atrial fibrillation (AF) and stroke. The usefulness of electrocardiographic indices in predicting stroke or systemic embolism (SSE) in patients undergoing cardioversion (CV) for AF remains unknown, especially in those at low estimated risk.

OBJECTIVE We systematically evaluated the performance of various P-wave abnormalities (PWAs) in predicting SSE 30 days after CV (derivation cohort) and in the long term (validation cohort).

METHODS Electrocardiograms (n = 1773) of AF patients undergoing an acute CV were manually reviewed. The 30-day post-CV data were used to derive a composite PWA variable. The electrocardiographic findings were validated by the long-term follow-up of patients with no anticoagulation. Electrocardiograms of 27 CAREBANK study patients with right atrial appendage biopsies were further analyzed for histopathologic validation.

RESULTS During data derivation, the best performance was found with a combination of prolonged P-wave (≥180 ms), deflected P-wave morphology in lead II, biphasic P-waves in inferior leads, or increased P-terminal force (≥80 mm·ms) as markers for extensive PWA. In the validation cohort, 219 of 874 (25.1%) had extensive PWA. During a median follow-up of 4.9 years, there were 51 patients (5.8%) with SSE in total. In a competing risk model, PWA predicted SSE (adjusted hazard ratio, 2.1 per category; 95% CI, 1.4–3.1; $P < .001$). Areas under the curve for SSE at 3 years were 0.77, 0.79, and 0.86 for PWA, CHA_2DS_2-VASc, score, and their combination, respectively. On histologic evaluation, extensive PWA was associated with interstitial fibrosis ($P = .033$).

CONCLUSION Novel electrocardiographic PWA classification provided additional prognostic insight in AF patients.

KEYWORDS Atrial fibrillation; Anticoagulation; Cardioversion; Electrocardiogram; P wave; Stroke

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Introduction

Atrial cardiomyopathy (aCM) is an electromechanical entity depicting abnormal atrial remodeling that has been suggested to propagate cardiac thrombogenesis and therefore to increase the risk for stroke or systemic embolism (SSE), even independently of atrial fibrillation (AF).[1,2] By definition, aCM reflects abnormal conduction, structure, and function of the atrial myocardium with the potential to cause clinically relevant manifestations. Despite being a well-known disease process, its electrocardiographic definition is poorly characterized.[1,3]

Surrogates for abnormal atrial remodeling may be visible on the 12-lead surface electrocardiogram (ECG) as P-wave abnormalities (PWAs), such as variations of the shape or duration. A bimodal shape of the P-wave or the increase in P-terminal force (PTF) is associated with left atrial enlargement,[4,5] whereas advanced interatrial block (AIAB) indicates dysfunction in the interatrial Bachmann bundle.[6] Elongated P-wave,[7] PTF,[8,9] and AIAB[10–12] have been linked to SSE independent of AF. An increase in P-wave duration has also been suggested to correlate with fibrosis in atrial biopsy

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specimens[13] as well as with low-voltage areas in intracardiac measurements.[14] In this study, we systematically analyze the significance of P-wave duration, different morphologies, and PTF in predicting SSE of nonanticoagulated AF patients. Furthermore, we explore the histopathologic findings underlying the electrocardiographic changes.

Methods

This study is a part of the Finnish Cardioversion (FinCV) protocol in progress to assess clinical challenges of AF (ClinicalTrials.gov identifier: NCT04001205).[15–18] Selection of patients has previously been described in detail.[15,16] The original patient cohort consists of 3143 individuals >18 years of age who underwent a cardioversion (CV) for acute (<48 hours) AF in 3 Finnish hospitals between 2003 and 2010. To be included in this substudy, a sinus rhythm ECG immediately after the index CV had to be available at Turku University Hospital through the local ECG database (MUSE Cardiology Information System 9.0; GE HealthCare, Chicago, IL). After the initial CV, follow-up data were collected until AF was deemed permanent, initiation of long-term (>4 weeks) oral anticoagulation therapy, or death. If there were no end point events, the follow-up ended on the date of the last entry in the patient record. Data on the date and cause of death were obtained from Statistics Finland, a governmental agency that reviews all death certificates issued in Finland.

The CHA_2DS_2-VASc score points were calculated according to the 2019 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society.[19]

ECG

Standard 12-lead ECGs (50 mm/s speed, 10 mm/mV voltage gain) were analyzed by a single observer blinded to the study outcomes. Measurements were made manually with digital magnification (up to 64×) but no calipers or other tools. Whereas line thickness was 0.15 mm, a precision of 0.25 mm (5 ms, 0.025 mV) was set for measurements, always rounding down. In a previous study, we ruled out the effect of possible effect of atrial stunning on the post-CV ECG.[17]

Abbreviations

aCM: atrial cardiomyopathy

AF: atrial fibrillation

AIAB: advanced interatrial block

CV: cardioversion

ECG: electrocardiogram

H&E: hematoxylin and eosin

PTF: P-terminal force

PWA: P-wave abnormality

SSE: stroke or systemic embolism

WvG: Weigert–van Gieson

P-wave duration was assessed from the limb leads by identifying the earliest and latest deviations from the baseline.[17] Multiple P-waves were measured, and the most representative duration was registered to account for signal noise and P-wave dispersion. PR interval was based on computerized calculation with visual checking for the integrity.

The morphology of the P-wave was assessed in lead II. Overall, 7 distinct P-wave patterns were identified by existing diagnostic criteria when applicable,[4–6,20] and distinctive properties were depicted for the rest (Table 1). Whenever multiple criteria were filled for a single P-wave, other complexes in lead II were observed and the best fitting morphology was chosen without preference to any pattern. In addition, all inferior leads were assessed for biphasic P-waves to diagnose AIAB. For AIAB, the biphasic pattern had to be most prevalent in inferior leads along with increased P-wave duration (≥120 ms).

PTF was defined as the product of duration and depth of the P-wave terminal portion in lead V_1. The terminal part initiated at first deflection below the baseline and ended when the upward deviation had a significant reduction in slope.

Left ventricular hypertrophy was calculated according to Sokolow-Lyon, Cornell, and modified Cornell criteria. If any of the criteria were met, left ventricular hypertrophy was considered present. Bundle branch blocks and their incomplete forms, fascicular blocks, and unspecified intraventricular conduction defects were diagnosed according to the consensus criteria.[5,21]

Study setting

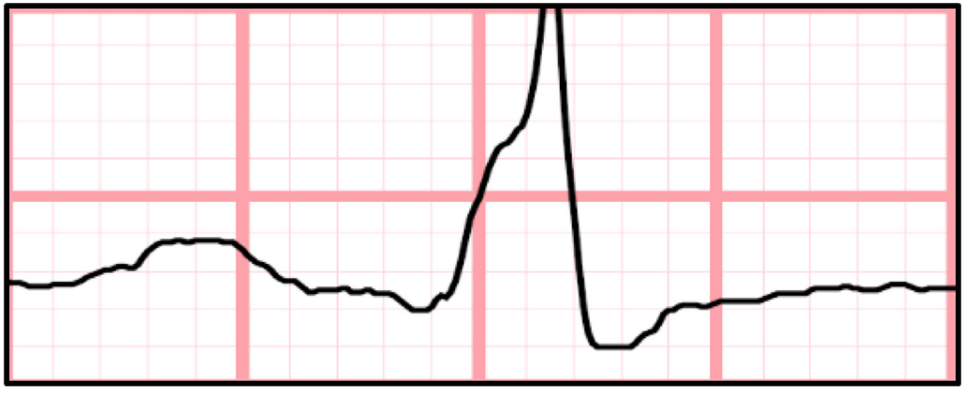
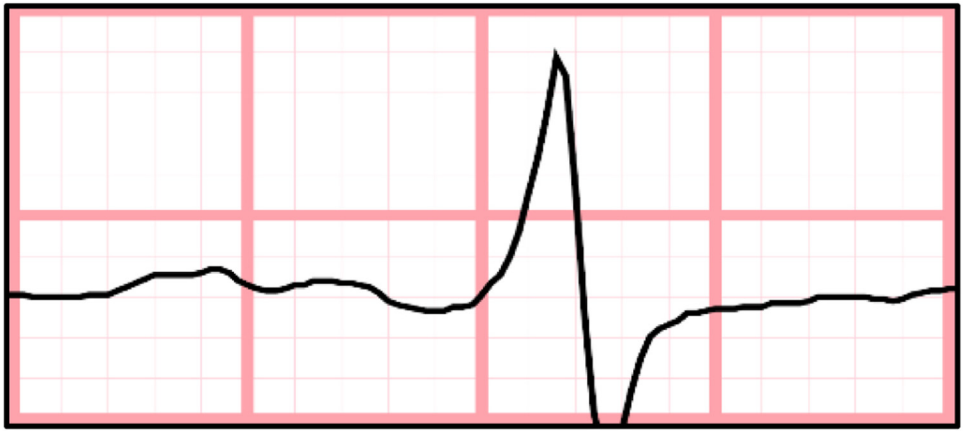
The study consists of data derivation and validation steps (Figure 1). In data derivation, we analyzed the power of various P-wave parameters on ECGs (n = 1313) to predict SSE in short-term (≤30 days) follow-up after CV regardless of anticoagulation status. We created a composite variable of PWA based on P-wave categories of <150 ms, 150–180 ms, and ≥180 ms, which were shown to correlate with intra-atrial low-voltage areas, contractile dysfunction, and thrombogenesis.[14,22] In addition, information on morphology and PTF was added to the categorization.

For the data validation cohort, we excluded all patients with long-term (>30 days) anticoagulation and short follow-up duration (≤30 days), leaving a total of 874 study participants. The main end point of the study was long-term SSE after the blanking period of 30 days after index CV. In addition, all other CV-related SSE events were excluded by censoring 30-day post-CV periods from analyses. SSE was defined as an ischemic stroke documented clinically and confirmed by computed tomography or magnetic resonance imaging or a systemic embolism confirmed by imaging, surgery, or autopsy. Secondary end points were all-cause death and incident heart failure.

Histopathologic analysis

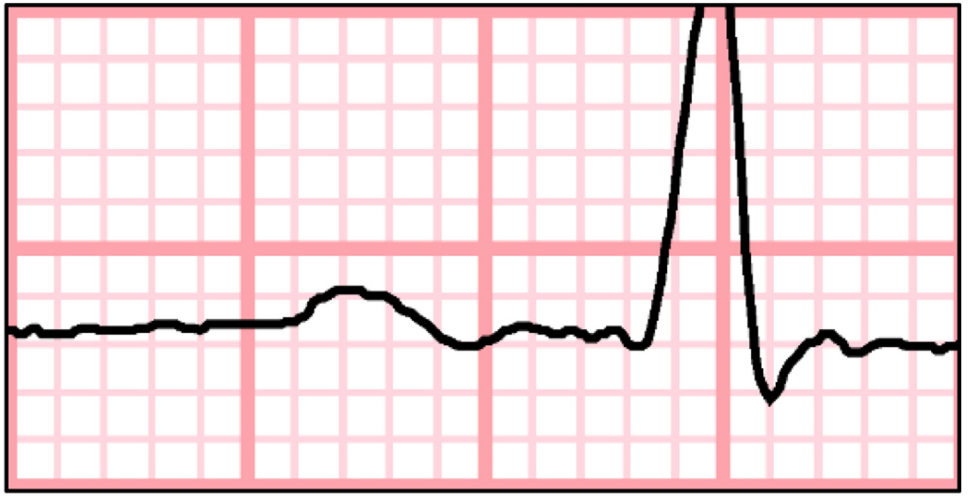
In addition to the FinCV data, we analyzed preoperative sinus rhythm ECGs of patients with paroxysmal AF (n = 27) from the CAREBANK (Cardiovascular Research Consortium—a Prospective Project to Identify Biomarkers of Morbidity and Mortality in Cardiovascular Interventional Patients) study. CAREBANK is an ongoing prospective study of patients undergoing cardiac surgery at Turku University Hospital (ClinicalTrials.gov identifier: NCT03444259). The full study methodology has previously been described in detail.[23,24] The protocol included recording preoperative ECGs and obtaining tissue biopsy specimens from the atrial appendage

Table 1 Variations in P-wave morphology

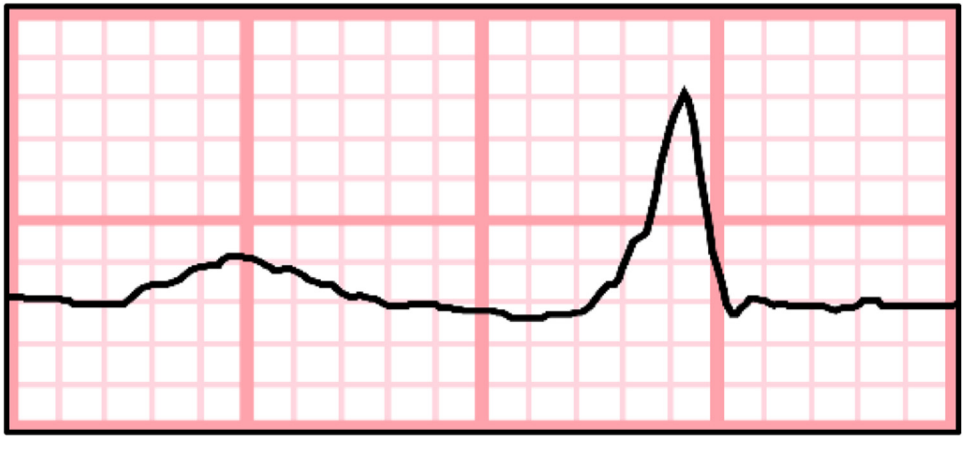
	Normal: a regular single-dome shape
	Bimodal (P mitrale): 2 distinct peaks, at least 40 ms apart

(*continued*)

Table 1 Continued

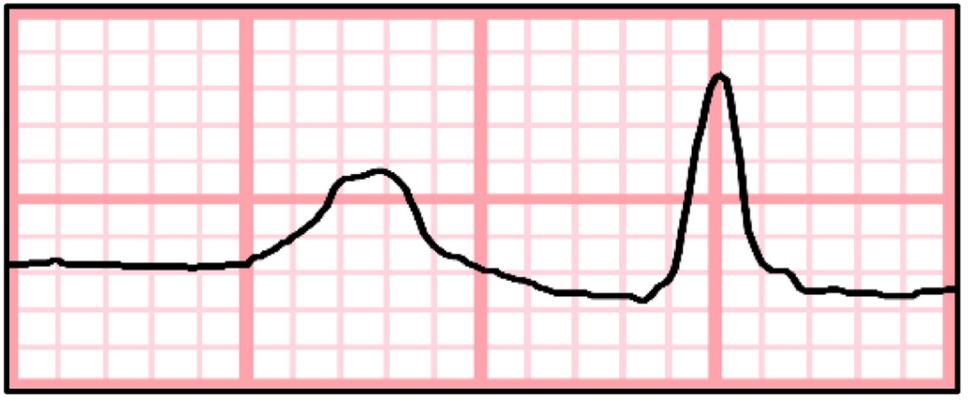
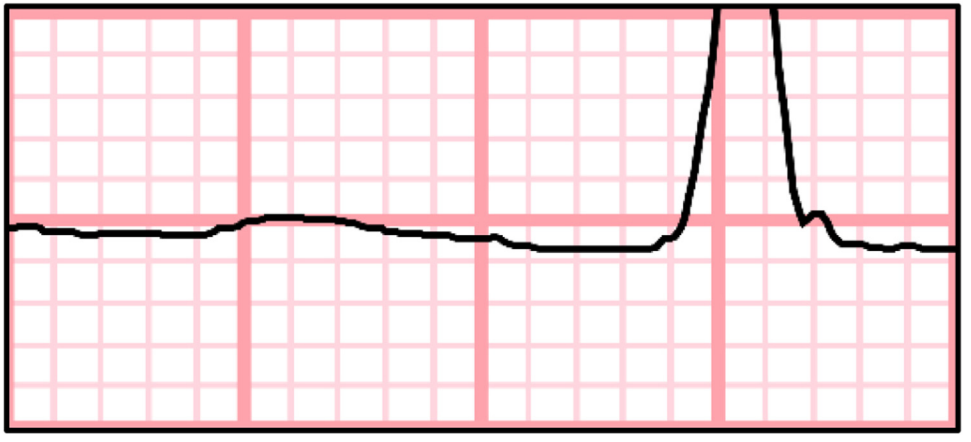


Biphasic: positive-negative or positive-negative-positive shape. The portion was considered negative if the deflection continued 40 ms under the baseline and ended with an upward deviation of at least 0.25 mm.



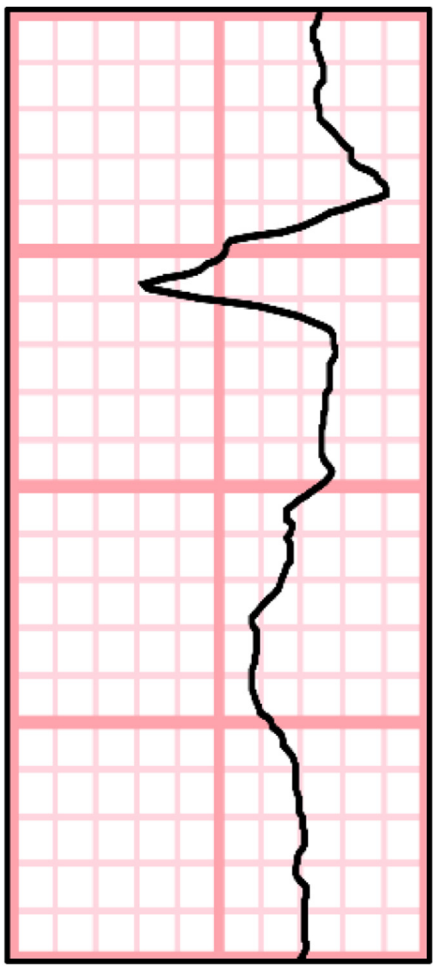
Tail: a convex terminal portion resembling a tail that consists of ≥50% P-wave total duration. The tail was measured from the point where the amplitude had halved from maximum until returning to baseline. Here, the total duration is 160 ms, of which the tail is 80 ms.

Table 1 Continued

	Peak (P pulmonale): domelike shape with amplitude ≥2.5 mm
	Flat: a smooth and usually long deviation from the baseline with maximum amplitude <0.5 mm

(*continued*)

Table 1 Continued

Deflected: a shape similar to bimodal, where a single distinct peak is followed by a flattened second peak. Interpeak distance is not measurable. Terminal part was considered a deflected peak if its amplitude was more than half of the maximum P-wave amplitude.	

Images are samples of standard electrocardiograms with 50 mm/s speed and 10 mm/mV voltage gain.

during the surgery. After extraction, samples were immediately frozen in −70°C, and cryosections of 5-μm slides were cut for staining. Hematoxylin and eosin (H&E) as well as Weigert–van Gieson (WvG) stainings were performed according to standardized protocols.

Specific scripts were made for detecting nuclei in H&E images and nuclei, fibrosis, and cardiomyocytes in WvG images by thresholding and particle selection features. Collagen total area was used as a measure for fibrosis. The data derived from the images were combined using R. Data are reported in arbitrary units. Average values of measurements from 4 randomly selected regions of interest were used for each patient.

Statistical analysis

Statistical analyses were conducted with SPSS version 25.0 software (IBM, Armonk, NY) and R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) using the "survival," "rms," and "timeROC" packages.

A 2-sided P value < .05 was considered statistically significant. Pearson χ^2 test, Fisher exact test, analysis of variance with Tukey test, Wilcoxon rank sum test, and Kruskal-Wallis test were used for univariate analyses, as appropriate. In Table 2, a Bonferroni correction was applied for groupwise testing.

A receiver operating characteristic (ROC) analysis was used to find a cutoff point for PTF in addition to the commonly used 40 mm·ms. Area under the curve (AUC) values were analyzed for creating the composite PWA variable. A time-dependent ROC analysis was used to compare the accuracy of variables predicting SSE at 3 years of follow-up. The optimal threshold for indicators was found with the Youden method.

Univariable logistic regression was used to assess the performance of different PWA models in derivation phase. In validation phase, multivariable logistic regression was applied to assess how PWA predicts heart failure as exact date for diagnosis was not available for time-dependent modeling. Kaplan-Meier analysis and Cox proportional hazards regression model were used to study the relationship between PWA and death. The association of PWA and SSE was analyzed with a competing risk model where death was the competing event. Multivariable models were adjusted for the CHA_2DS_2-VASc score calculated at the time of CV.

Data reliability

A random sample of 25 patients had the ECG reexamined to analyze intraobserver reliability. For continuous variables, the intraclass correlation coefficient varied between 0.85 and 0.96 (P < .001); Cohen κ for categorical variables varied between 0.75 and 0.84 (P < .001).

Study ethics

The FinCV and CAREBANK studies received approvals from the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. The studies conform to the Declaration of Helsinki. Informed consent was obtained

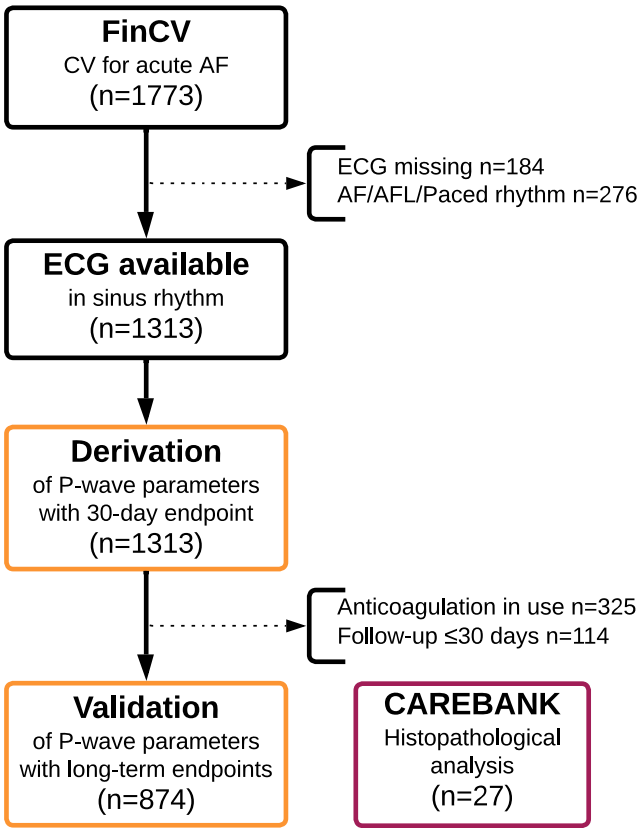


Figure 1
Study setting. Post-cardioversion (CV) electrocardiograms (ECGs) were analyzed from patients undergoing acute CV for atrial fibrillation (AF). During data derivation, potential P-wave parameters were tested for short-term stroke or systemic embolism association and the composite variable for P-wave abnormality (PWA) was constructed. The predictive power of PWA was validated with long-term stroke or systemic embolism as well as with heart failure and death in nonanticoagulated patients. The histologic properties of PWA were assessed in a separate CAREBANK study population. AFL = atrial flutter; FinCV = Finnish Cardioversion protocol.

from the participants of the CAREBANK study but was not required for FinCV patients because of the retrospective nature of the study. Data underlying this article are available on a reasonable request to the corresponding author.

Results

Derivation cohort

During the 30-day follow-up, a total of 17 (1.3%) SSE events occurred. ECG samples from SSE patients are presented in Supplemental Figure 1. The SSE patients were more often older and hypertensive and had higher CHA_2DS_2-VASc scores. Detailed clinical and electrocardiographic characteristics for the patient groups are shown in Supplemental Table 1.

In univariate analyses, patients with SSE had a trend for longer P-wave duration as well as for higher prevalence of AIAB and a deflected P-wave morphology. The relationship between PTF and SSE was statistically significant, and the optimal cutoff value for PTF was 80 mm·ms with 58.3% sensitivity and 89.5% specificity in the ROC analysis. P-wave duration categories alone were not significant in predicting SSE with odds ratio (OR) of 1.8 (95% CI, 1.0–3.4; $P = .05$) and AUC of 0.62, whereas adding morphology and PTF categories to the model significantly improved the performance to OR of 2.9 (95% CI, 1.4–5.9; $P = .003$) and AUC of 0.70. The patients were assigned to 3 groups: no PWA (n = 472 [35.9%]), moderate PWA (n = 521 [39.7%]), and extensive PWA (n = 320 [24.4%]). The complete algorithm for classification is presented in Figure 2.

In extensive, moderate, or no PWA groups, the rates for SSE were 10 (3.0%), 5 (1.0%), and 2 (0.4%; $P = .003$), respectively. In a multivariable logistic regression model, PWA predicted 30-day SSE (adjusted OR, 2.7; 95% CI, 1.3–5.5; $P = .007$).

Validation cohort

The final population consisted of 874 nonanticoagulated patients with follow-up duration >30 days. The median follow-up time was 4.9 (1.7–9.9) years, during which 51 (5.8%) patients suffered from SSE, 25 (2.9%) received a new heart failure diagnosis, and 232 (26.5%) died. Clinical and electrocardiographic characteristics classified by long-term SSE occurrence are shown in Supplemental Table 1.

On the ECG, PWA was a common finding as 207 (23.7%) patients had extensive PWA and 328 (37.5%) had moderate PWA. The prevalence of each diagnostic P-wave criterion in corresponding PWA groups is shown in Supplemental Figure 2. Baseline characteristics and follow-up details for PWA categories are presented in Table 2, showing that PWA was associated with greater cardiovascular burden and higher CHA_2DS_2-VASc score.

Rates of SSE per 100 person-years were 2.7, 0.68, and 0.45 in respective extensive, moderate, and no PWA groups. The ROC curves comparing the performance of PWA, CHA_2DS_2-VASc score, and their combination in classifying patients with SSE at 3 years are presented in Supplemental Figure 3. In a multivariable competing risk analysis, PWA was a significant risk factor for SSE (hazard ratio [HR], 2.1; 95% CI, 1.4–3.1; $P < .001$) after adjustment for the CHA_2DS_2-VASc score (HR, 1.2; 95% CI, 1.1–1.4; $P < .001$; Figure 3A). Similarly, in a multivariable Cox regression model predicting death, PWA (HR, 1.3; 95% CI, 1.1–1.5; $P = .007$) and CHA_2DS_2-VASc (HR, 1.8; 95% CI, 1.6–1.9; $P < .001$) were significant (Figure 3B). The multivariable logistic regression model for incident heart failure was significant for PWA (OR, 2.1; 95% CI, 1.2–3.7; $P = .007$), but not the CHA_2DS_2-VASc score (OR, 1.2; 95% CI, 0.9–1.5; $P = .18$).

In a subgroup analysis consisting of 511 patients with CHA_2DS_2-VASc scores of 0 or 1, there were 16 (3.1%) SSE events. These events were most common in the extensive PWA group (n = 7 [7.6%]), whereas moderate PWA (n = 6 [3.1%]) and no PWA (n = 3 [1.3%]) were less affected ($P = .02$). Cumulative incidence functions for SSE as well as Kaplan-Meier curves for death are presented in Figure 4. Similarly, in patients with 0 CHA_2DS_2-VASc points, 4 of 43 (9.3%) with extensive PWA, 2 of 106 (1.9%) with moderate PWA, and 2 of 145 (1.4%) with no PWA suffered from SSE ($P = .02$).

Table 2 Baseline and follow-up characteristics grouped by electrocardiographic P-wave abnormality classification

	P-wave abnormality					
	No PWA (n = 339)	Moderate PWA (n = 328)	Extensive PWA (n = 207)	P^a	P^b	P^c
Baseline						
Age	60 (50–69)	62 (54–69)	67 (58–74)	<.001	.24	<.001
≥65 years	123 (36.3)	134 (40.9)	119 (57.5)	<.001	.70	<.001
≥75 years	44 (13.0)	41 (12.5)	50 (24.2)	<.001	>.99	.003
Female sex	141 (41.6)	101 (30.8)	71 (34.3)	.01	.01	.31
Hypertension	121 (35.7)	138 (42.1)	102 (49.3)	.007	.29	.007
Heart failure	8 (2.4)	21 (6.4)	8 (3.9)	.03	.04	.93
Diabetes	22 (6.5)	40 (12.2)	20 (9.7)	.04	.04	.56
Vascular disease	45 (13.3)	51 (15.5)	50 (24.2)	.003	>.99	.005
Prior stroke or TIA	8 (2.4)	15 (4.6)	13 (6.3)	.07	.42	.11
CHA_2DS_2-VASc	1 (0–3)	1 (0–3)	2 (1–3)	<.001	.08	<.001
≥2	115 (33.9)	133 (40.5)	115 (55.6)	<.001	.24	<.001
Antiarrhythmic drugs[d]	164 (48.7)	197 (60.8)	141 (68.1)	<.001	.006	<.001
Ventricular block	30 (8.9)	40 (12.3)	29 (14.5)	.12	.50	.19
LVH	25 (7.4)	40 (12.2)	36 (17.4)	.002	.11	.001
End of follow-up						
Duration, y	6.9 (2.6–10.9)	4.6 (1.6–10.9)	3.5 (1.2–8.1)	<.001	.03	<.001
No. of CVs performed	2 (1–4)	2 (1–3)	1 (1–3)	.02	.21	.02
Heart failure	6 (1.8)	5 (1.5)	14 (6.8)	<.001	>.99	.01
Myocardial infarction	18 (5.3)	16 (4.9)	14 (6.8)	.64	>.99	>.99
Death	71 (20.9)	81 (24.7)	80 (38.6)	<.001	.80	<.001
SSE	11 (3.3)	13 (4.0)	27 (13.0)	<.001	>.99	<.001
At 3 years	1 (0.3)	4 (1.2)	9 (4.3)	<.001	.63	.003
At 5 years	5 (1.5)	8 (2.4)	16 (7.7)	<.001	>.99	.001
CHA_2DS_2-VASc	2 (1–3)	2 (1–3)	3 (1–4)	<.001	.92	<.001
≥2	197 (58.1)	208 (63.4)	154 (74.4)	<.001	.53	<.001

Data are reported as median (interquartile range) or count (percentage), as appropriate.
CVs = cardioversions; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category (female); LVH = left ventricular hypertrophy; SSE = stroke or systemic embolism; PWA = P-wave abnormality; TIA = transient ischemic attack.
[a]Difference between all the groups.
[b]Bonferroni corrected comparison of no PWA and moderate PWA.
[c]Bonferroni corrected comparison of no PWA and extensive PWA.
[d]Data missing on 6 cases.

Histopathology

We obtained histologic data along with sinus rhythm ECGs from 27 patients with known history of AF in the CAREBANK study. All patients had both H&E- and WvG-stained slides available. In this subset, there were 7 (26%) patients with extensive PWA, 6 (22%) with moderate PWA, and 14 (52%) with no PWA. There was a significant ($P = .03$) difference in total fibrosis area between the PWA groups in analysis of variance; and in post hoc testing, extensive PWA was associated with greater fibrosis area than in those with no PWA (mean [SD] area, $61.7 \cdot 10^4$ [$11.1 \cdot 10^4$] AU vs $36.0 \cdot 10^4$ [$4.8 \cdot 10^4$] AU; $P = .03$; for visual assessment, see Figure 5). Comparison between extensive and moderate PWA ($36.0 \cdot 10^4$ [$13.9 \cdot 10^4$] AU) remained nonsignificant ($P = .09$). The number or the size of the nuclei did not significantly differ between the groups (data not shown).

Discussion

The unique FinCV database originating before introduction of the CHA_2DS_2-VASc score allowed us to evaluate SSE risk of nonanticoagulated AF patients with varying risk profiles. Our findings show that electrocardiography provides additional information on susceptibility for SSE, heart failure, and death. Compared with no PWA, patients with extensive PWA had nearly 4-fold risk for SSE and 2-fold risk for death, even after adjustment for the CHA_2DS_2-VASc score. Similarly, the odds for heart failure were tripled. To our knowledge, no other study has reviewed atrial changes on the ECG to this extent in an attempt to enhance risk stratification of patients with AF.

Various studies have explored the viability of ECGs in predicting clinical outcomes, usually focusing on only a few parameters at the same time.[25] A multicenter study used the ECGs of nearly 500,000 patients to assess the relationship of automatically measured P-wave elongation (≥120 ms) and SSE in AF-naive patients but neglected other P-wave indices completely.[7] The association was clear regardless of CHA_2DS_2-VASc score, similar to our work. Nevertheless, PTF[8,9] or biphasic morphology[10–12] was not considered in the risk assessment. Maheshwari and coworkers[26] investigated fine-tuning SSE risk stratification by adding extra points to CHA_2DS_2-VASc score for having various P-wave parameters present. Whereas AIAB and PTF predicted SSE, only

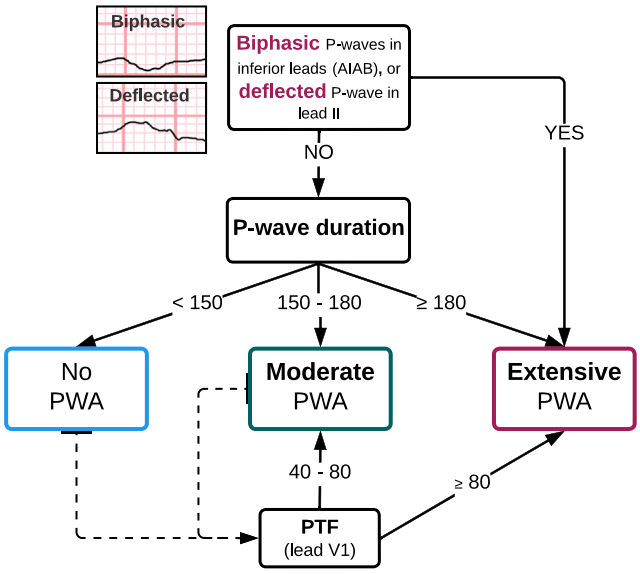


Figure 2
Patient categorization algorithm. Patients were assigned to categories according to P-wave length and morphology as well as P-terminal force (PTF). P-wave durations are shown in milliseconds and PTF values in millimeters·milliseconds. AIAB = advanced interatrial block; PWA = P-wave abnormality.

abnormal P-wave axis improved the C statistic when combined with the clinical score. The improved model had a modest C statistic of 0.75 at best for 1-year stroke prediction, whereas our 3-year model was significantly greater with a C statistic (AUC) of 0.86.

Unlike the risk for SSE, incident heart failure is a less reported end point in electrocardiography-related research. Such connection has been reported for P-wave elongation[7] and PTF.[27] Similarly, the prevalence of elongated P-waves and AIAB seems to be higher in patients with heart failure[10] (21% and 24%) than in the general population[12] (10% and 1%). Finally, risk for all-cause or cardiac death has been associated with elongated P-waves,[7] AIAB,[10] and PTF.[27] Eranti and coworkers[27] found that greater PTF (≥60 mm·ms) was a better predictor for death than the conventional (≥40 mm·ms) value.

PWA seems to be much more prevalent in AF patient cohorts compared with the general population.[17] In the present FinCV cohort, 6% had AIAB and 40% had PTF ≥40 mm·ms, when only 1% of healthy individuals have AIAB and 3%–8% have abnormal PTF.[12,27,28] It has been postulated that atrial remodeling and aCM may precede AF and work as a substrate predisposing to future rhythm disturbances.[1–3] AF in turn keeps the remodeling process ongoing.

The consensus report defines aCM as a multifactorial process that includes conduction blocks, atrial enlargement, and fibrosis.[3] The underlying processes of aCM have been suggested to increase risk for SSE even without presence of AF, making easy identification of aCM a compelling topic for research. Our composite P-wave analysis gathers, at least theoretically, information on all these abnormal atrial properties. However, owing to lack of concrete evidence, we refrained from naming the electrocardiographic parameters "markers of aCM." The basis of our PWA variable was P-wave duration categorization by Müller-Edenborn and colleagues[14,22] that was found to be associated with intracardiac low-voltage areas as well as with atrial thrombi in echocardiography and adverse cardiac and cerebrovascular events. Strikingly, the prevalence of PWA was similar, unlike in AF-naive populations as described before, which might be partly explained by the high degree of ECG amplification. Whereas the number of adverse events was low (63/218 [29%]) in their follow-up, the risk profiles were similar to ours, further emphasizing the results. In addition, in our cohort, the patients with extensive PWA were significantly older and more likely to

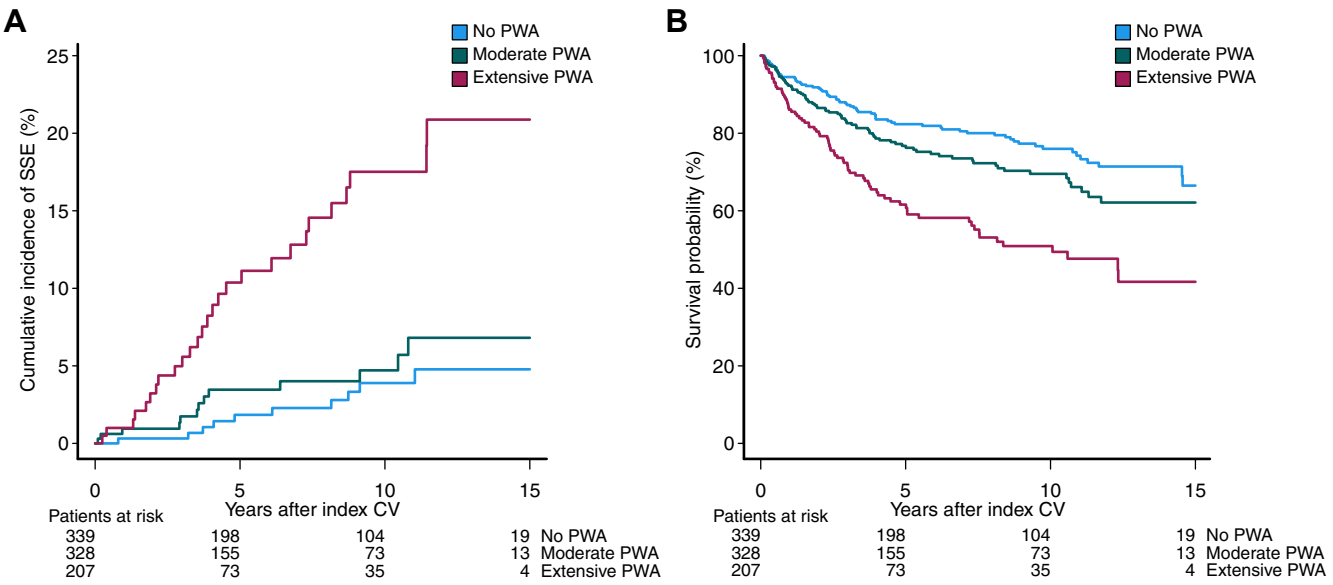


Figure 3
Outcomes according to P-wave abnormality (PWA) categorization. Cumulative incidence function of stroke or systemic embolism (SSE) in a Fine-Gray model where death is the competing risk (**A**) and Kaplan-Meier survival analysis (**B**). CV = cardioversion.

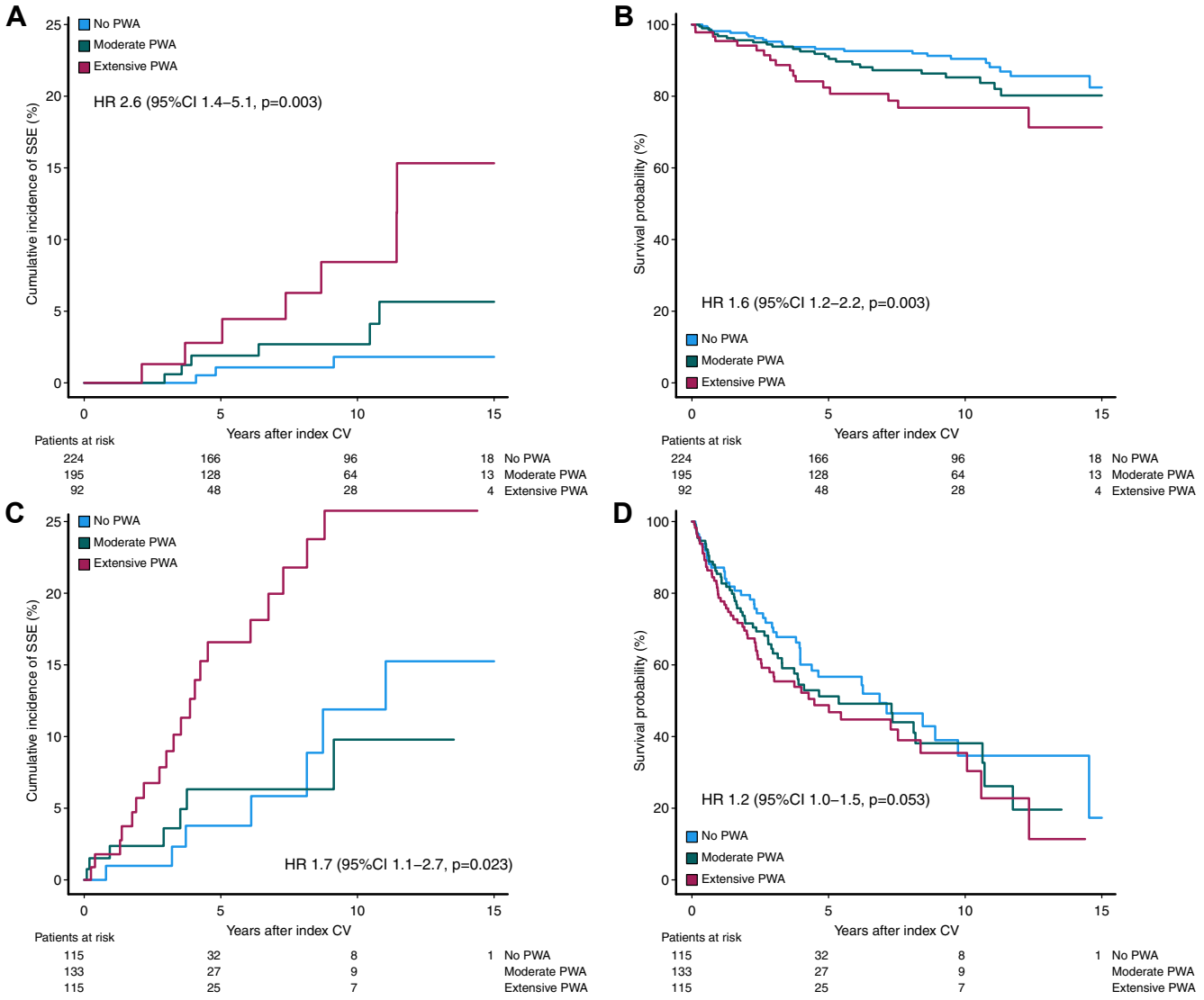


Figure 4

Outcomes according to P-wave abnormality (PWA) categorization in subgroup analyses. **A, B:** Patients with CHA_2DS_2-VASc score <2. **C, D:** Patients with CHA_2DS_2-VASc score ≥2. **A** and **C** present cumulative incidence function of stroke or systemic embolism (SSE) in a Fine-Gray model where death is the competing risk. **B** and **D** present Kaplan-Meier survival analysis. CI = confidence interval; CV = cardioversion; HR = hazard ratio.

have higher cardiovascular disease burden, which could be driving forces to this degenerative process of the atria (Table 2). These findings highlight the idea that atrial remodeling is a multifactorial process that acts over time.

This study relies on the assumption that electrocardiographic changes relating to aCM are due to underlying atrial pathologic processes, such as fibrosis and conduction blocks, and would be nonregressing during the follow-up. It is, however, unknown how fast these changes come into sight and whether new abnormalities developed during the follow-up period. Earlier studies suggest that aged populations have longer P-wave durations, but no progression was observed during a 3-year period.[29,30] In one study, P-wave duration, AIAB, and PTF were found to be labile markers over time[28]; however, the possibly transient nature of AIAB-like aberrations of the QRS complex[6] was not considered. In this respect, it is noteworthy that patients with extensive PWA had higher extent of myocardial fibrosis in atrial biopsy specimens from the CAREBANK study. This suggests that electrocardiographic changes of extensive PWA not only are related to left atrial hypertrophy and altered electrical coupling of cardiomyocytes but are at least partly fibrotic in origin and therefore might not be reversible. Unfortunately, information on the atrial size was unavailable for this study. The longitudinal evolution and potential reversibility of PWA findings on the ECG require additional research.

Clinical implications

Our results indicate that the ECG may provide additional information in considering oral anticoagulation to prevent AF-related SSE in borderline cases. Current guidelines recommend that oral anticoagulation should be considered if a patient has a single CHA_2DS_2-VASc point, and treatment should be withheld when the patient presents with no risk

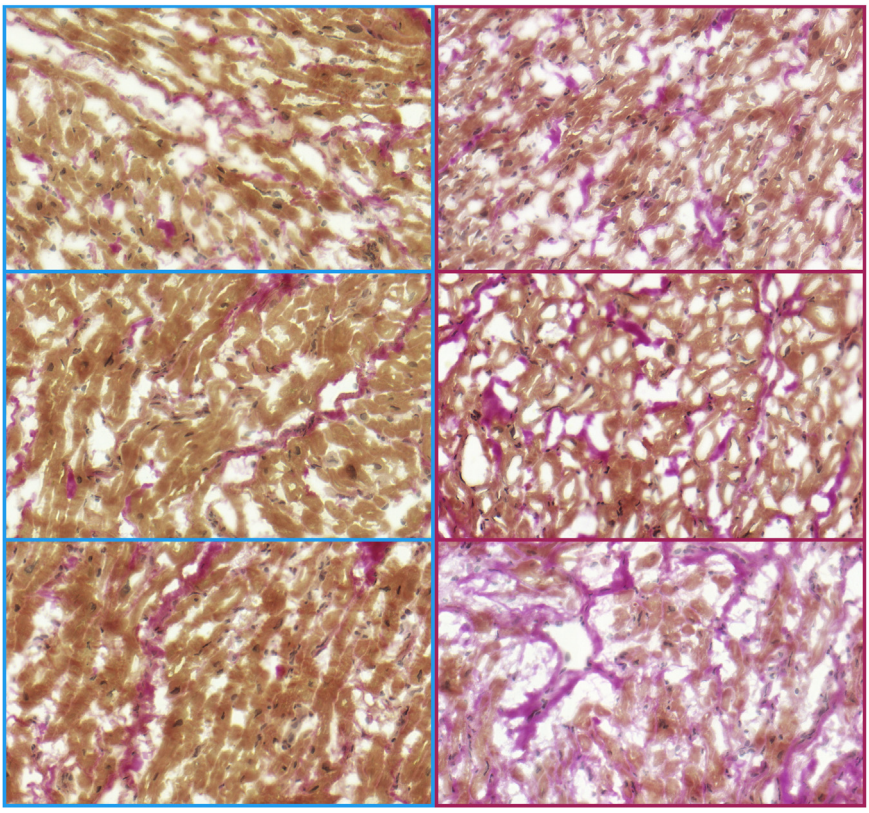


Figure 5
Histopathologic analysis. Weigert–van Gieson–stained samples from right atrial appendage biopsies. Normal myocardium is stained *brown* and fibrous tissue *purple*. Panels on the left were obtained from patients with no P-wave abnormality; panels on the right represent extensive P-wave abnormality.

score.[19] In our data, patients with extensive PWA were at higher risk for SSE regardless of the clinical score. CV temporarily increases the risk of SSE, and postprocedural anticoagulation is considered according to the duration of the AF episode and CHA_2DS_2-VASc score.[18] We suggest that electrocardiographic markers of extensive PWA should be acknowledged in considering long-term oral anticoagulation after CV in patients who according to CHA_2DS_2-VASc score are at borderline risk for SSE.

Limitations

The main limitation of the study is the retrospective setting of FinCV. However, data were gathered from electronic patient records by a structured case report form to ensure uniformity. In addition to local records, information on causes of deaths was obtained from the national registry Statistics Finland. Because of the study setting of analyzing post-CV ECGs in sinus rhythm, patients with unsuccessful CV were naturally excluded. Nevertheless, there were no other exclusion criteria that would have affected the SSE outcomes. Regardless of the excluded participants, the investigation consisted of derivation and validation phases with nearly 900 patients.

Conclusion

PWA provided additional prognostic insight on risk of SSE in patients with AF. This electrocardiographic information may be useful in considering anticoagulation in borderline cases.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.04.083.

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