Excessive Premature Atrial Complexes and the Risk of Recurrent Stroke or Death in an Ischemic Stroke Population

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Background: Our aim was to investigate the association of premature atrial complexes and the risk of recurrent stroke or death in patients with ischemic stroke in sinus rhythm. *Methods:* In a prospective cohort study, we used 24-hour Holter recordings to evaluate premature atrial complexes in patients consecutively admitted with ischemic strokes. Excessive premature atrial complexes were defined as >14 premature atrial complexes per hour and 3 or more runs of premature atrial complexes per 24 hours. During follow-up, 48-hour Holter recordings were performed after 6 and 12 months. Among patients in sinus rhythm, the association of excessive premature atrial complexes and the primary end point of recurrent stroke or death were estimated in both crude and adjusted Cox proportional hazards models. We further evaluated excessive premature atrial complexes contra atrial fibrillation in relation to the primary end point. *Results:* Of the 256 patients included, 89 had atrial fibrillation. Of the patients in sinus rhythm (n = 167), 31 had excessive premature atrial complexes. During a median follow-up of 32 months, 50 patients (30% of patients in sinus rhythm) had recurrent strokes (n = 20) or died (n = 30). In both crude and adjusted models, excessive premature atrial complexes were associated with the primary end point, but not with newly diagnosed atrial fibrillation. Compared with patients in atrial fibrillation, those with excessive premature atrial complexes had similarly high risks of the primary end point. *Conclusions:* In patients with ischemic stroke and sinus rhythm, excessive premature atrial complexes were associated with a higher risk of recurrent stroke or death. **Key Words:** Atrial fibrillation—ischemic stroke—prognosis—premature atrial complexes.

Introduction

Stroke is related to severe disabilities and a high risk of stroke recurrence and death.[1,2] A major risk factor is atrial fibrillation (AF),[3] which may, if paroxysmal, be difficult to diagnose. AF is thought to be triggered by atrial ectopic beats originating predominantly from the area around the pulmonary veins.[4] Such premature atrial complexes (PACs) presenting singly or as short runs are common findings on electrocardiograms (ECGs) and are typically considered harmless. However, they have recently been investigated in both healthy adults and patients with stroke for the prediction of subclinical AF.

Increased atrial ectopic activity has been shown to be correlated with increased risk of AF,[5-9] although no causal relationship has been demonstrated. Among healthy adults,

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a correlation was found between excessive PACs (ePACs) and stroke, beyond incident AF,[10] and with a high risk of death,[11,12] but the prognostic impact of PACs in patients with ischemic stroke is not fully elucidated. In particular, it is unknown whether the prognosis for patients with ischemic stroke with PACs is the same as that for patients with ischemic stroke and AF.[3]

The aim of the study was to investigate whether increased atrial ectopic activity is associated with an increased risk of death, recurrent stroke, and AF in patients with ischemic stroke and sinus rhythm (SR), and to compare prognoses in patients with high burdens of PACs and patients with AF.

Methods

Study Design

This prospective single-center observational cohort study complies with the Declaration of Helsinki and was approved by the regional Ethics Committee. Before inclusion, all patients gave written informed consent directly or through a surrogate when appropriate. The study was registered at Clinicaltrials.gov with the unique identifier NCT02180542.

Patients

Patients admitted to this study were >18 years and admitted with acute ischemic stroke at the stroke unit of Svendborg Hospital from 2012 to 2014. Strokes were defined according to the criteria of the World Health Organization,[13] and patients were included within 96 hours of stroke onset. Hemorrhagic and ischemic strokes were distinguished based on computed tomography and magnetic resonance imaging scans. Patients with hemorrhagic strokes were excluded. Further exclusion criteria are listed in Figure 1.

Each patient underwent a 12-lead ECG. As part of standard care, patients presenting in SR underwent 48 hours of continuous inpatient cardiac telemetry (CICT) to detect AF. To evaluate PACs, each patient without AF had a subsequent 24-hour Holter recording (Spacelabs Healthcare Lifecard CF, Issaquah, WA) performed 2-4 days after enrollment. In addition, a standard transthoracic echocardiography study was performed in all patients.

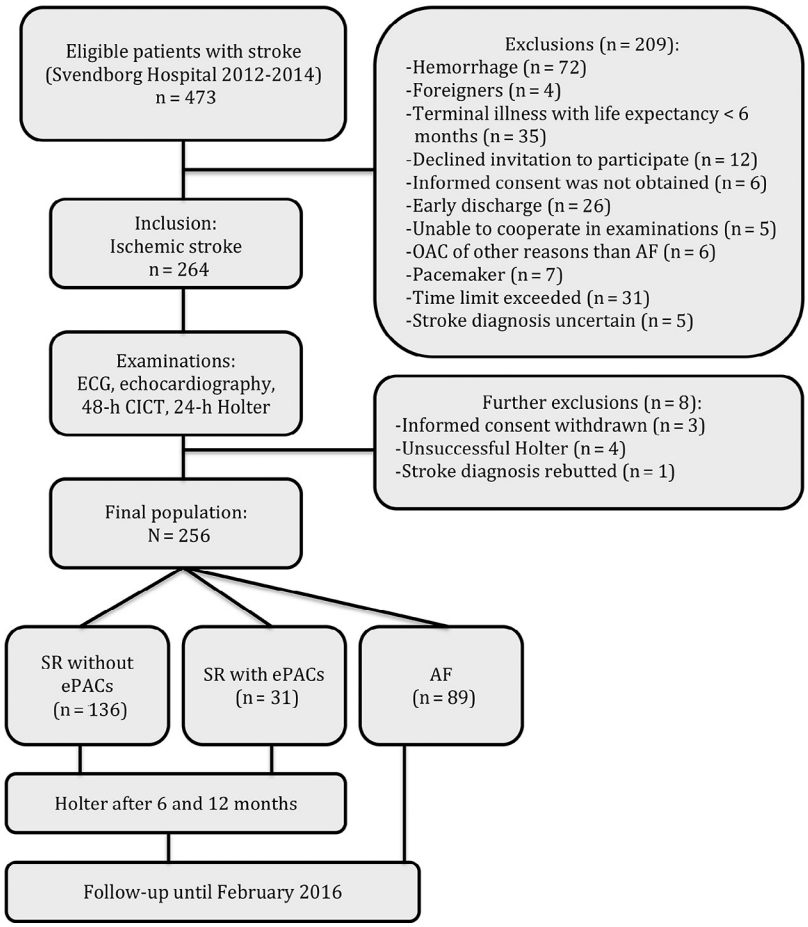

Figure 1. *Method flowchart.* Abbreviations: *AF, atrial fibrillation; CICT, continuous inpatient cardiac telemetry; ECG, echocardiogram; ePACs, excessive PACs; OAC, oral anticoagulant treatment; PAC, premature atrial complex; SR, sinus rhythm.*

Patients who were found not to have had strokes and those with unsuccessful Holter recordings were later excluded from further evaluation (Fig 1).

Information on baseline characteristics was assessed from interviews and from patient records with respect to medical history and medical status.

Stroke severity was evaluated according to the Scandinavian Stroke Scale (SSS) and reflected the clinical condition at the time of maximum impairment within the first 4 days from admission. The SSS is a validated neurological stroke scale in Scandinavia that evaluates stroke severity. The scores range from 0 to 58, with 58 indicating a normal score.[14] Patients were stratified into 2 groups according to stroke severity. A severe stroke was defined as an SSS score of ≤25, and a mild-to-moderate stroke was defined as an SSS score of >25, as previously used by others.[15]

Holter Recordings and Definitions

Analyses of the baseline Holter recordings were conducted by 1 experienced observer blinded to patient data using Spacelabs Healthcare Pathfinder SL, an automated program. All automatically detected events were manually reviewed and reclassified if necessary.

Two categories of atrial ectopic activity were studied: runs of PACs, defined as 3 or more consecutive PACs, with an accelerated cycle length lasting <30 seconds; and number of isolated PACs. An isolated PAC was defined as a complex with a premature P (the coupling interval to the preceding QRS complex had to be ≤75% of the mean RR interval of basic rhythm before the event) and with a QRS complex similar or identical to those of the normal sinus beats.

Additionally, if AF was registered, anticoagulant treatment was initiated if not contraindicated. AF was defined according to the guidelines of the American College of Cardiology/American Heart Association and with duration of ≥30 seconds.[16]

We defined ePACs from a cutoff set at the top quartile for both the number of runs of PACs and the frequency of PACs. This definition is frequently used by others with regard to the frequency of PACs.[6,7,17] Accordingly, ePACs were defined as >14 PACs per hour and 3 or more runs of PACs per 24 hours.

Patients were divided into 3 groups according to their heart rhythm: patients with AF (patients with a history of AF, AF on the initial ECG, CICT, or baseline Holter), patients in SR with ePACs, and patients in SR without ePACs.

Follow-Up

Patients were followed until February 2016 or until death. To screen for AF during follow-up, 48-hour Holter recordings were performed after 6 and 12 months from enrollment. The Holter analyses were conducted by trained and experienced technicians who were blinded to patient data.

The study was designed with a combined end point, taking the size of our population into account. The primary end point was death or recurrent stroke. Recurrent stroke was defined as either a recurrent ischemic stroke or a transient ischemic attack. The secondary end points were death, recurrent stroke, and AF, respectively.

Information on new occurrences of AF, recurrent stroke, and death within the follow-up period was retrieved from the medical records and discharge summaries of our hospital and other institutions, and from Holter analyses during follow-up.

Statistical Analysis

Distributions of baseline characteristics in the 3 groups were summarized and compared pairwise using the chi-square test for categorical variables and the *t*-test for continuous variables.

We carried out a survival analysis comparing patients in SR with ePACs from the top quartiles with those of the bottom 3 quartiles (SR without ePACs). Kaplan–Meier survival estimators and the log-rank test were used to investigate the risk of recurrent stroke or death in the 2 groups. A Cox proportional hazards model was used to estimate the hazard ratios (HR) of ePACs in relation to the primary end point and to the end point of death in crude and adjusted models. To determine the association between ePACs and the end point of recurrent stroke and AF, respectively, the Fine–Gray regression model was used, with death treated as a competing risk.[18] Covariates used for the adjusted models were age, sex, previous stroke, hypertension, diabetes, coronary artery disease, stroke severity, left ventricular ejection fraction, and left atrial end diastolic volume indexed on body surface area (LAEDV).

All the models were adjusted for age and sex. Other covariates were entered into the model only if they had $P \leq .1$ in a univariate analysis. The included covariates are specified under each table. All analyses were repeated, including only patients with mild-to-moderate ischemic strokes. Furthermore, we repeated all analyses, including number of PACs per 24 hours (as a continuous variable on a log scale) or runs of PACs (as a dichotomous variable) as a predictor instead of ePACs.

Finally, in an adjusted Cox regression model, we compared the risk of the primary end point in the ePACs group and the AF group.

In all survival analyses, we used Schoenfeld residuals to verify the proportional hazard assumption and checked interaction terms when appropriate. *P* values <.05 were considered statistically significant. To evaluate the inter- and intra-rater variability, we produced Bland–Altman plots to compare the Holter measurements produced by 2 raters.

Statistical analyses were performed using STATA, version 14.1 IC (StataCorp LP, College Station, TX).

Results

Of the 437 eligible patients, 209 were excluded according to the exclusion criteria (Fig 1). We included 264 patients in the study, but 8 were excluded from further evaluation (Fig 1). Of the remaining 256 patients, 89 were diagnosed with AF (n = 64 with known AF, n = 14 with AF at ECG, n = 8 with AF at CICT, and n = 3 with AF at baseline Holter). All patients in SR (n = 167) had complete 24-hour Holter recordings during admission. Of the patients presenting in SR at discharge and without known AF, there were 83 (50%) patients who had runs of PACs. The number of PACs per 24 hours was represented with a median of 49 (interquartile range, 13-347), and patients with ePACs (n = 31) comprised 19% of the patients in SR.

Baseline characteristics are summarized in Table 1. Patients in SR with ePACs were older, had more severe strokes, had a higher total CHA2DS2-VASc score, and had a markedly enlarged left atrial volume than did patients in SR without ePACs (Table 1).

During a median follow-up of 32 months (interquartile range, 23-40), 34 patients in SR died and 20 had a recurrent stroke. No patients were lost to follow-up. The primary end point of recurrent stroke or death occurred in 50 patients, and the Kaplan–Meier survival curve (Fig 2) showed a greater number of events among patients with ePACs than in those without. According to the log-rank test, the difference between the groups was statistically significant ($P = .014$).

In the Cox regression analysis, ePACs were associated with recurrent stroke or death in both crude and adjusted models (Table 2). The total number of PACs was statistically significant in the crude model and in

Table 1. *Baseline characteristics of ischemic stroke patients*

		A	B	C	*P*	
	All (n = 256)	SR without ePACs (n = 136)	SR with ePACs (n = 31)	AF (n = 89)	*A* > < *B*	*B* > < *C*
Male sex	141 (55)	84 (62)	17 (55)	40 (45)	.477	.342
Age, y	73 ± 12.6	68 ± 12.7	78 ± 8.3	80 ± 9.4	<.001	.236
Comorbidity:						
Previous stroke	84 (33)	43 (32)	8 (26)	33 (37)	.526	.254
CAD	34 (13)	16 (12)	2 (6)	16 (18)	.389	.122
Diabetes mellitus	34 (13)	22 (16)	2 (6)	10 (11)	.164	.444
Hypertension	145 (57)	77 (57)	17 (55)	51 (57)	.857	.812
SSS score	42.4 ± 15.3	45.9 ± 13.0	39.6 ± 15.9	38.1 ± 17.1	.022	.670
SSS score > 25	221 (86)	125 (92)	27 (87)	69 (78)	.397	.251
BMI (kg/m^2)	25.9 ± 4.3	26.5 ± 4.2	24.6 ± 4.0	25.5 ± 4.5	.021	.342
Smoking (%)	76 (30)	55 (40)	8 (26)	13 (15)	.143	.252
Hypercholesterolemia	98 (28)	49 (36)	9 (29)	40 (45)	.460	.121
Antithrombotics	66 (26)	35 (26)	7 (23)	24 (27)	.715	.631
OAC at discharge	77 (30)	2 (1)	0 (0)	75 (84)	—	—
CHA_2DS_2-VASc*	4.64 ± 1.34	4.21 ± 1.32	4.87 ± 1.18	5.24 ± 1.19	.011	.142
HAS-BLED†	2.42 ± .77	2.28 ± .80	2.55 ± .72	2.62 ± .70	.089	.637
Time of monitoring, h	65.4 ± 19.9	65.8 ± 18.0	68.2 ± 23.1	55.5 ± 26.4	.533	.104
Echocardiographic characteristics						
LVEF, %	51.2 ± 12.4	53.5 ± 11.1	55.0 ± 8.0	46.5 ± 14.1	.531	.004
IVSd, cm	1.27 ± .35	1.24 ± .32	1.32 ± .36	1.29 ± .38	.269	.697
LAEDV, mL/m^2	30.6 ± 14.4	23.9 ± 8.9	31.2 ± 18.0	40.6 ± 14.3	.003	.007
E/E'	8.95 ± 4.7	8.2 ± 3.9	8.5 ± 4.1	10.2 ± 5.8	.758	.165

Abbreviations: CAD, coronary artery disease; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke, Vascular disease, Age, and Sex; HAS-BLED = Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile international normalized ratio, Elderly, Drugs or alcohol; IVSd, interventricular septal diameter; LAEDV, left atrial end diastolic volume indexed on body surface area; LVEF, left ventricular ejection fraction; OAC, oral anticoagulant treatment; PAC, premature atrial complex; SSS, Scandinavian Stroke Scale.

Values are mean ± SD and n (%).

*CHA_2DS_2-VASc score at discharge counts 2 points each for previous stroke or transient ischemic attack and age ≥ 75 years, and 1 point each for age 65-74 years, heart failure, hypertension, diabetes mellitus, vascular disease, and female sex.

†HAS-BLED score at discharge counts 1 point each for hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly (age ≥ 65), drugs or alcohol concomitantly.

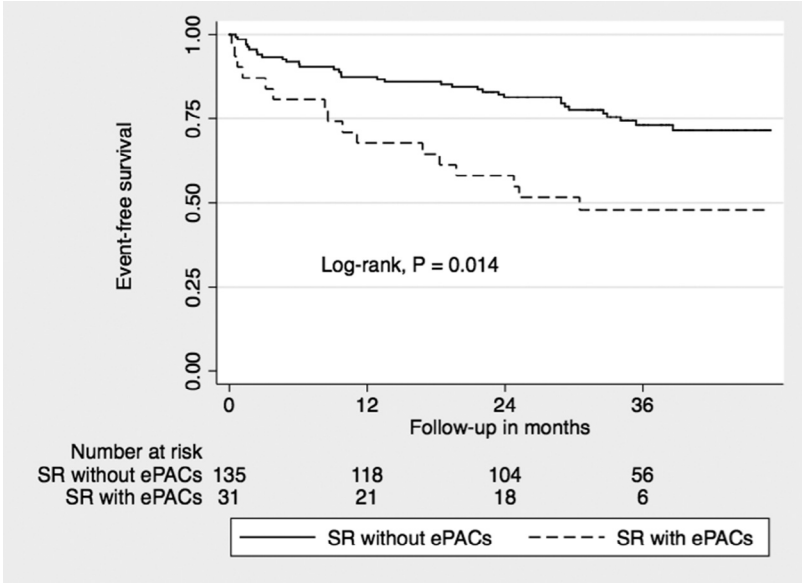

Figure 2. *Kaplan–Meier survival curve of recurrent stroke or death-free survival in patients with and without ePACs.* Abbreviations: *ePACs, excessive PACs; PAC, premature atrial complex; SR, sinus rhythm; TIA, transient ischemic attack.*

the adjusted model, including only patients with mild-to-moderate ischemic stroke. The association of the predictor variable runs of PACs and the primary end point was not statistically significant in any of the models (Table 2).

For the end point of death, ePACs were associated with death in the crude model. In the adjusted model, there was a tendency toward an association of ePACs and the risk of death, and this association was confirmed in the adjusted model, including only patients with mild-to-moderate ischemic stroke (Table 2). Number of PACs and runs of PACs were similarly associated with the primary end point in both the crude model and the adjusted model, excluding patients with severe strokes.

For the end point of recurrent stroke, patients with ePACs tended to have a higher risk of having the event than patients without, but the result was not statistically significant in any of the models.

Incident AF during follow-up was diagnosed in only 9 patients, 2 of whom were diagnosed from the Holter recordings. Only 62% of patients in SR completed both Holter recordings during follow-up. There was a tendency

Table 2. *Cox regression models showing the risk of recurrent stroke or death and death in relation to PACs*

	Recurrent stroke or death		Death	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Crude model				
ePACs	2.55 (1.41-4.63)	.002	3.84 (1.94-7.61)	<.001
No. of PACs/24 h‡	1.22 (1.09-1.37)	.001	1.33 (1.16-1.53)	<.001
Runs of PACs	1.41 (.81-2.47)	.224	2.81 (1.34-5.87)	.006
Model 1*				
ePACs	1.89 (1.00-3.49)	.049	2.06 (.97-4.35)	.059
No. of PACs/24 h‡	1.13 (.99-1.30)	.071	1.14 (.96-1.34)	.136
Runs of PACs	1.17 (.66-2.06)	.590	1.85 (.87-3.92)	.111
Model 2†				
ePACs	2.20 (1.13-4.24)	.019	3.61 (1.53-8.51)	.003
No. of PACs/24 h‡	1.19 (1.03-1.37)	.021	1.26 (1.05-1.51)	.014
Runs of PACs	1.26 (.68-2.33)	.467	3.17 (1.26-8.01)	.038

Abbreviations: ePACs, excessive PACs; HR, hazard ratio; PAC, premature atrial complex; SSS, Scandinavian Stroke Scale.

*The model was adjusted for age, sex, and stroke severity for the end point of recurrent stroke or death, and for age, sex, stroke severity, and coronary artery disease for the end point of death.

†The model included only patients with mild and moderate ischemic stroke (SSS >25) (n = 153), and was adjusted for age and sex for the end point of recurrent stroke or death, and for age, sex, and coronary artery disease for the end point of death.

‡Number of PACs per 24 hour presented as HR per 1 unit on a log scale.

Table 3. *Competing risks model showing the risk of AF in the follow-up in relation to PACs, with death as a competing risk*

	Crude model		Adjusted model*	
	SHR (95%CI)	*P*	SHR (95%CI)	*P*
ePACs	3.55 (.98-12.8)	.053	3.05 (.70-13.3)	.136
PACs/24 h‡	1.29 (1.04-1.60)	.018	1.24 (.89-1.73)	.211
Runs of PACs	2.18 (.57-8.36)	.257	1.24 (.27-5.63)	.779

Abbreviations: AF, atrial fibrillation; ePACs, excessive PACs; LVEF, left ventricular ejection fraction; PAC, premature atrial complex; SHR, subdistribution hazard ratio.

*Adjusted for age, sex, and LVEF.

‡Number of PACs per 24 hour presented as SHR per 1 unit on a log scale.

toward an association of ePACs with development of AF in both crude and adjusted models, but it was not statistically significant (Table 3).

LAEDV was not associated with end points in any of the univariate analyses. Including LAEDV in the adjusted models did not change the results. Furthermore, no interaction was found between ePACs and LAEDV.

Patients in SR with ePACs and those with AF were almost comparable according to age and stroke severity, but echocardiographic features of left ventricular ejection fraction and LAEDV were significantly different. Patients with ePACs had smaller LAEDVs and, in general, less comorbidity. Of patients diagnosed with AF, 84% were treated with oral anticoagulant treatment (OAC) at discharge (Table 1). Cox regression models comparing the primary end point for patients with ePACs and AF did not show a statistically significant difference between the 2 groups (crude: HR = .83 [.47-1.48], $P = .532$; adjusted: HR = .84 [.47-1.50], $P = .549$).

In regard to the Holter analyses, the Bland–Altman plot revealed good intra- and inter-rater agreement. The limits of agreement all contained zero, indicating no systematic bias in measurements.

Discussion

In this prospective study of patients with ischemic stroke, ePACs were found to be associated with a higher risk of recurrent stroke or death in patients with SR. Furthermore, we found that the characteristics and prognoses in terms of recurrent stroke or death of patients with ePACs approximated those of patients with AF.

In general, the definition of frequent PACs is not well defined. Different cutoffs have been used to define frequencies of PACs, and not all studies include runs of PACs.[8,19,20] We tried to approach an excessive burden of PACs, and the classification of runs of PACs and frequent PACs in the present study is in line with the definitions used by Kochhäuser et al.[7]

To our knowledge, this is the first prospective study investigating ePACs in relation to death or recurrent ischemic stroke among patients with stroke. When studying stroke survival, both AF and stroke severity were found to be independent predictors of death.[21] In the present study, we found ePACs to be associated with recurrent stroke or death, even when adjusted for stroke severity. In the subgroup analysis excluding patients with severe stroke, this association was even more robust. This result is important because it is well known that patients with severe stroke, compared with those with mild-to-moderate ischemic stroke, have a higher mortality risk[21] or suffer more severe disabilities, making secondary prevention less clinically relevant. Furthermore, we found runs of PACs to be associated with death in the subgroup analysis, which is in line with results from a retrospective study performed in a large ischemic stroke population.[22]

Moreover, we found an association between the number of PACs per 24 hours and the end points, which further shows consistency in our results.

Our findings indicate that having ePACs is a marker or a possible mediator of ischemic stroke or death, but the mechanism is unclear. The most likely underlying mechanism is that ePACs are precursors or markers of subclinical paroxysmal AF, as suggested by others.[7,8,23] However, we did not find a statistically significant association between ePACs and the incidence of AF during follow-up. The lack of statistical power could be an explanation for the nonsignificant association, because only 9 patients had AF during follow-up. Moreover, we had already diagnosed 11 patients with AF from carefully performed cardiac monitoring (CICT and Holter) at the stroke unit, whereas, in comparison, most previous studies reported up to 24-hour monitoring after a stroke.[8,24] Additionally, with respect to the larger LAEDV in patients with ePACs, compared with patients without ePACs, we cannot rule out that the presence of ePACs could be only a marker of heart disease and cardiovascular mortality.

Currently, only AF and atrial flutter have been viewed as causing ischemic stroke and, therefore being an indication for considering OAC treatment,[25] whereas PACs typically have been considered harmless. The results in the present study indicate that patients with high burdens of atrial electric instability, such as ePACs, may resemble patients with AF more than formerly assumed. Patients with ePACs even tended to have higher risks of the primary end points than do patients with AF, and this was despite a smaller LAEDV, less severe strokes, and no marked dissimilarities in comorbidity. However, this comparison is limited by the frequent use of OAC in the AF group, and because the ePACs group likely did not receive anticoagulation, the result must be interpreted with caution. Nevertheless, it raises the issue of whether patients with ePACs are candidates for OAC.

Limitations

This study had several limitations. With the prospective observational study design, selection bias cannot be excluded, even though only a few patients were unwilling to participate. However, with the surrogate consent, even patients with acute severe disability could participate in the study. The cutoff set for ePACs was arbitrary because an accepted cutoff does not exist. However, similar cutoffs used for PACs were found to be diagnostically useful in former studies among patients with stroke.[7,9] Another limitation of the study is the small number of events, which limits both the power to detect associations and the ability to control completely for all potential confounders in the adjusted analyses. Although a wide range of prognostic factors were evaluated in the analyses and no patients were lost to follow-up, the possibility that residual confounding could have influenced the results cannot be excluded. Finally, the incidence of AF was very likely underestimated, because not all patients completed the outpatient monitoring scheduled during follow-up. Accordingly, additional AF registration was evaluated in the medical records in regard to medical status and admissions with AF, with full knowledge that such a method is also prone to result in an incomplete identification of AF, especially subclinical AF.

Conclusion

In a population of patients with ischemic stroke, ePACs were associated with a higher risk of recurrent stroke or death among patients in SR. In regard to patient characteristics, patients with ePACs resembled patients with AF. The evaluation of ePACs might contribute to the selection of patients for prolonged cardiac rhythm monitoring to detect AF, but to determine whether such patients are candidates for OAC treatment, randomized studies are warranted.

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References

1. Hankey GJ, Jamrozik K, Broadhurst RJ, et al. Long-term risk of first recurrent stroke in the Perth Community Stroke Study. Stroke 1998;29:2491-2500.
2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015;131:e29-e322.
3. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996;27:1760-1764.
4. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-666.
5. Binici Z, Intzilakis T, Nielsen OW, et al. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation 2010;121:1904-1911.
6. Chong BH, Pong V, Lam KF, et al. Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. Europace 2012;14:942-947.
7. Kochhäuser S, Dechering DG, Dittrich R, et al. Supraventricular premature beats and short atrial runs predict atrial fibrillation in continuously monitored patients with cryptogenic stroke. Stroke 2014;45:884-886.
8. Wallmann D, Tuller D, Wustmann K, et al. Frequent atrial premature beats predict paroxysmal atrial fibrillation in stroke patients: an opportunity for a new diagnostic strategy. Stroke 2007;38:2292-2294.
9. Weber-Kruger M, Groschel K, Mende M, et al. Excessive supraventricular ectopic activity is indicative of paroxysmal atrial fibrillation in patients with cerebral ischemia. PLoS ONE 2013;8:e67602.
10. Larsen BS, Kumarathurai P, Falkenberg J, et al. Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident atrial fibrillation. J Am Coll Cardiol 2015;66:232-241.
11. Lin CY, Lin YJ, Chen YY, et al. Prognostic significance of premature atrial complexes burden in prediction of long-term outcome. J Am Heart Assoc 2015;4:e002192.
12. Qureshi W, Shah AJ, Salahuddin T, et al. Long-term mortality risk in individuals with atrial or ventricular premature complexes (results from the Third National Health and Nutrition Examination Survey). Am J Cardiol 2014;114:59-64.
13. Stroke—1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke 1989;20:1407-1431.
14. Lindenstrom E, Boysen G, Christiansen LW, et al. Reliability of Scandinavian Neurological Stroke Scale. Cerebrovasc Dis 1991;1:103-107.
15. Christensen H, Fogh Christensen A, Boysen G. Abnormalities on ECG and telemetry predict stroke outcome at 3 months. J Neurol Sci 2005;234:99-103.
16. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2011;123:e269-e367.
17. Suzuki S, Sagara K, Otsuka T, et al. Usefulness of frequent supraventricular extrasystoles and a high CHADS2 score to predict first-time appearance of atrial fibrillation. Am J Cardiol 2013;111:1602-1607.
18. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
19. Pinho J, Braga CG, Rocha S, et al. Atrial ectopic activity in cryptogenic ischemic stroke and TIA: a risk factor for recurrence. J Stroke Cerebrovasc Dis 2015;24:507-510.
20. Todo K, Moriwaki H, Saito K, et al. Frequent premature atrial contractions in stroke of undetermined etiology. Eur Neurol 2009;61:285-288.
21. Andersen KK, Andersen ZJ, Olsen TS. Predictors of early and late case-fatality in a nationwide Danish study of 26,818 patients with first-ever ischemic stroke. Stroke 2011;42:2806-2812.

22. Vinther KH, Tveskov C, Moller S, et al. Prevalence and prognostic significance of runs of premature atrial complexes in ischemic stroke patients. J Stroke Cerebrovasc Dis 2016;25:2338-2343.
23. Weber-Kruger M, Gelbrich G, Stahrenberg R, et al. Finding atrial fibrillation in stroke patients: randomized evaluation of enhanced and prolonged Holter monitoring—Find-AF(RANDOMISED)—rationale and design. Am Heart J 2014;168:438-445, e1.
24. Gladstone DJ, Dorian P, Spring M, et al. Atrial premature beats predict atrial fibrillation in cryptogenic stroke: results from the EMBRACE trial. Stroke 2015;46:936-941.
25. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-2236.