

# Prevalence and Prognostic Significance of Runs of Premature Atrial Complexes in Ischemic Stroke Patients

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*Background and Purpose:* Runs of premature atrial complexes (PACs) are common in stroke patients and perceived to be clinically insignificant, but their prognostic significance is unclear. This study investigated the association between runs of PACs in ischemic stroke patients and the risk of recurrent ischemic strokes/transient ischemic attacks (TIAs) or death. *Methods:* The study included consecutive patients admitted with an ischemic stroke from August 2008 to April 2011. Patients with known and newly detected atrial fibrillation were excluded. Runs of PACs were defined as 3 or more PACs lasting less than 30 seconds during 48 hours of continuous inpatient cardiac telemetry. The patients were followed for 4 years or until death, whichever came first. They were stratified according to stroke severity. The combined primary endpoint was a recurrent ischemic stroke/TIA or death. *Results:* Of the 565 patients included in the study, 28% had runs of PACs. Patients with runs of PACs were likely to be older, female, and to have experienced more severe strokes. During the follow-up, 210 (37%) patients had a recurrent ischemic stroke/TIA (n = 73) or died (n = 137) respectively. Among the 489 patients who had mild-to-moderate strokes, runs of PACs were associated with recurrent ischemic strokes/TIAs or death (hazard ratio = 1.47; 95% CI 1.06-2.04; P = .023). *Conclusion:* Runs of PACs were frequent in patients with acute ischemic strokes and sinus rhythm, and they were independently associated with an increased risk of recurrent ischemic strokes/TIAs or death in patients with mild-to-moderate strokes. **Key Words:** Atrial fibrillation—cardiac monitoring—ischemic stroke—prognosis—premature atrial complexes.

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## Introduction

Strokes are the second-leading cause of death worldwide, and often leave survivors permanently disabled, resulting in large socioeconomic costs.<sup>1</sup> The most severe ischemic strokes tend to be in patients with atrial fibrillation (AF),<sup>2</sup> which is a well-known risk factor for ischemic stroke.<sup>3,4</sup> Cohort studies of healthy individuals and stroke patients have shown that both excessive premature atrial complexes (PACs) and short runs of PACs are risk factors for having or developing AF.<sup>5-9</sup> Nevertheless, no causal relationship has been demonstrated between excessive PACs/runs of PACs and AF, and it is unknown whether the prognosis of ischemic stroke patients with PACs is the same as that of ischemic stroke patients with AF.<sup>2</sup>

Runs of PACs of less than 30 seconds have been recorded among stroke patients.<sup>6,10</sup> These are perceived to be clinically insignificant, but their prognostic value is unknown. To determine the potential prognostic significance of runs of PACs in ischemic stroke patients without AF, this study investigated the association between the prevalence of runs of PACs and the risk of recurrent ischemic strokes/transient ischemic attacks (TIAs) or death.

## Methods

### *Population and Cardiac Monitoring*

This was a retrospective cohort study, including patients with an acute stroke and who were consecutively admitted to the stroke unit at Odense University Hospital Svendborg between August 1, 2008 and April 1, 2011. The patients were identified in the Danish Stroke Registry (DSR), which is a nationwide validated database set up to monitor the quality of care in stroke patients.<sup>11</sup> Participation is mandatory for all Danish hospitals that treat acute stroke. Strokes were defined according to the criteria of the World Health Organization.<sup>12</sup> Hemorrhagic and ischemic strokes were distinguished based on computed tomography and magnetic resonance imaging scans, and all patients with hemorrhagic strokes were excluded.

Information on the heart rhythm was evaluated reviewing patient telemetric records and patient records. To identify silent AF, all patients with a suspected stroke and without known AF routinely underwent an electrocardiogram (ECG) on admission, followed by 48 hours of continuous inpatient cardiac telemetry (CICT). During admission, a cardiologist reviewed the ECG and CICT and reported whether runs of PACs and AF had occurred. Runs of PACs were defined as 3 or more consecutive PACs, with an accelerated cycle length lasting less than 30 seconds. AF was defined according to the guidelines of the American College of Cardiology/American Heart Association as an arrhythmia lasting 30 seconds or more.<sup>13</sup> Patients with a history of AF, AF on the initial ECG or CICT, or absence of telemetry data were excluded. Patients without a Danish civil registration number were also excluded. The included patients were divided into those with and without runs of PACs. Additional baseline data on the following were obtained from the DSR: previous stroke, hypertension, diabetes mellitus, previous myocardial infarction (MI), and Scandinavian Stroke Scale (SSS) score. The SSS is a validated and widely used neurological stroke scale in Scandinavia that evaluates the stroke severity on a score ranging from 0 to 58, where 58 indicates a normal score.<sup>14</sup> A severe stroke was defined as an SSS score of less than or equal to 25, and a mild-to-moderate stroke was defined as an SSS score of more than 25, as previously used by others.<sup>15</sup> The risk factors were all reported within 24 hours of admission.

### *Follow-Up*

Follow-up started on the day of admission or the date of stroke occurrence if the patient was already hospitalized with another diagnosis. All the patients were followed up for 4 years or until death, whichever came first.

Data on incident AF, recurrent ischemic strokes/TIAs, and death were obtained from discharge letters from the hospital, the national Civil Registration System, and patient records. The Civil Registration System is a national database with personal information on individuals who are resident in Denmark. All data are reported within 2 weeks. Patient records were surveyed to register any admissions to other hospitals in the country during the study period.

The primary combined endpoint was a recurrent ischemic stroke/TIA or death. Further endpoints were death, a recurrent ischemic stroke/TIA, and AF. The study was approved by the Board of the DSR, the Danish Data Protection Agency, and the Danish Health and Medicines Authority, and was registered at [Clinicaltrials.gov](https://clinicaltrials.gov) with the ID: NCT02610803.

### *Statistical Analysis*

Continuous variables with a normal distribution were compared using a *t*-test. The data are presented as means  $\pm$  standard deviation. Data not normally distributed were compared using the Kruskal–Wallis test, and the data are presented as medians, with interquartile ranges. A chi-square test was used for a comparison of categorical variables.

The Kaplan–Meier survival estimator was used to model the risk of recurrent ischemic strokes/TIAs or death in the 2 groups, and the log-rank test was used to test whether there were any differences between the groups. A Cox proportional hazards model was used to estimate the hazard ratios of runs of PACs in relation to the primary combined endpoint and to the endpoint of death in crude and adjusted models.

To determine the association between runs of PACs and the endpoint of recurrent ischemic stroke/TIA, and AF, the Fine–Gray regression model was used, with death treated as a competing risk.<sup>16</sup>

All the models were adjusted for age and sex. Other covariates were only entered into the model if  $P \leq .1$  in a univariate analysis. The included covariates are specified under each table. The analyses were restricted to patients without missing values. All analyses were repeated including only patients with mild-to-moderate ischemic strokes, as we expected patients in the 2 SSS score groups to have markedly dissimilar mortality rates during follow-up. The Kaplan–Meier survival estimator was used to estimate mortality rates according to stroke severity. We used Schoenfeld residuals to verify the proportional hazard assumption and performed stratified analyses when appropriate. *P* values  $< .05$  were considered statistically significant. Statistical analyses were

performed using STATA, version 14.1 IC (StataCorp LP, College Station, Texas, USA).

**Results**

Of the 971 consecutive patients with a stroke, 863(89%) had an ischemic stroke. The following patients were excluded: 3 (.3%) who resided outside Denmark; 225 (26%) with AF; and 70 (8%) with absent telemetry data, resulting in a final ischemic stroke cohort of 565 patients.

One-hundred sixty-one (28%) patients with runs of PACs were detected by 48-hour CICT. The baseline characteristics of the patients with and without runs of PACs are shown in Table 1. The patients with runs of PACs were likely to be older and female; had lower rates of diabetes mellitus, hypertension, previous MI, and previous stroke; and had lower median SSS scores (Table 1).

During 4 years of follow-up, 158 (28%) patients died, 73 (13%) had a recurrent ischemic stroke/TIA, and 210 (37%) had a combined outcome of recurrent ischemic stroke/TIA or death. For the combined endpoint of recurrent stroke/TIA or death, the Kaplan–Meier survival curve (Fig 1) showed a greater number of events among patients with than without runs of PACs. According to the means of the log-rank test, the difference between

the groups was statistically significant. In the Cox regression analysis, the runs of PACs were correlated with recurrent ischemic strokes/TIAs or death in the crude but not the adjusted model, although there was a tendency toward an association of runs of PACs and the endpoints detected in the latter (Table 2). By including only patients with mild-to-moderate ischemic strokes, an independent association between runs of PACs and an increased risk of recurrent ischemic strokes/TIAs or death was confirmed (Table 2). To examine whether one of the events drew the combined endpoint, we made additional analyses for the endpoint of death and recurrent ischemic stroke/TIA, respectively. For the endpoint of death, runs of PACs were associated with death in the crude model. In the adjusted model, there was a tendency toward an association of runs of PACs and the risk of death, and this association was confirmed in the adjusted model including only patients with mild-to-moderate ischemic strokes (Table 2). For the endpoint of recurrent ischemic stroke/TIA, patients with runs of PACs had a higher risk of having the event than patients without runs of PACs, but the result was not statistically significant either for the crude, the adjusted, or the model including only patients with mild-to-moderate ischemic strokes (Table 3).

Only 45 patients had severe stroke. The 1-month and 1-year mortality rates in those patients were 35% and 75%, respectively.

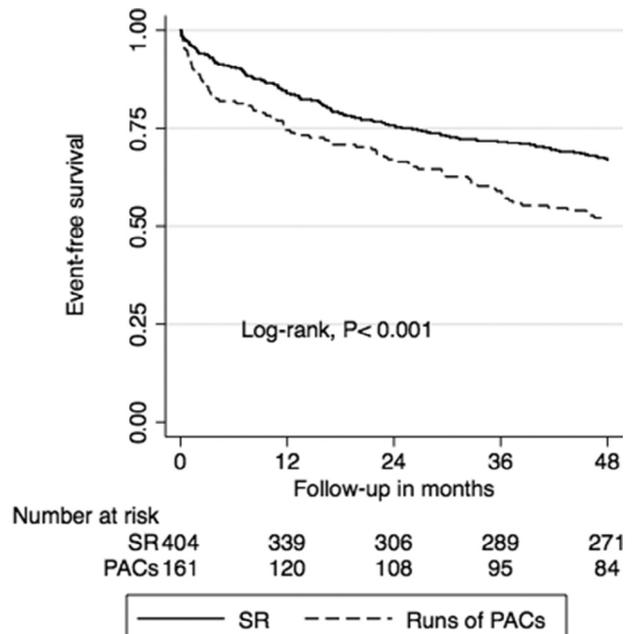
AF was observed in 22 patients during the follow-up, representing 5% of patients with runs of PACs and 3.5% of patients without runs of PACs. Hypertension, but not

**Table 1.** Baseline characteristics of ischemic stroke patients in sinus rhythm, with and without runs of PACs

	Ischemic stroke (n = 565)		P value
	Without runs of PACs (n = 404)	With runs of PACs (n = 161)	
Female sex	165 (40)	87 (54)	.004
Age (year)	69.9 ± 13.5	75.4 ± 9.9	<.001
Previous stroke			
Yes	77 (19)	23 (14)	.172
Missing	14 (3)	5 (3)	
Previous MI			
Yes	31 (8)	11 (7)	.714
Missing	8 (2)	2 (1)	
Diabetes mellitus			
Yes	53 (13)	8 (5)	.005
Missing	9 (2)	4 (2)	
Hypertension			
Yes	180 (45)	57 (35)	.055
Missing	18 (4)	9 (6)	
SSS score	52 (11)	50 (16)	.0012
Missing	11 (3)	3 (2)	
SSS score >25	366 (93)	137 (87)	.016
Time of CICT (h)	47 (14)	48 (21)	<.001

Abbreviations: CICT, continuous inpatient cardiac telemetry; MI, myocardial infarction; PAC, premature atrial complex; SSS, Scandinavian Stroke Scale.

Values are mean ± standard deviation, n (%), or median (interquartile range).



**Figure 1.** Kaplan–Meier survival estimate of recurrent ischemic strokes/TIAs or death-free survival in patients, with and without runs of PACs. SR indicates patients without runs of PACs. Abbreviations: PAC, premature atrial complex; TIA, transient ischemic attack.

**Table 2.** Cox regression models showing the risk of recurrent ischemic strokes/TIAs or death and death in relation to runs of PACs and other risk factors

	Recurrent ischemic stroke/TIA or death		Death	
	HR (95% CI)	P	HR (95% CI)	P
Crude model				
Runs of PACs	1.63 (1.23-2.15)	.001	1.79 (1.30-2.47)	<.001
Adjusted model*				
Runs of PACs	1.32 (.98-1.78)	.068	1.39 (.99-1.96)	.059
Age	1.04 (1.03-1.06)	<.001	1.07 (1.06-1.09)	<.001
Male sex	1.27 (.95-1.07)	.111	—	—
Previous stroke	1.45 (1.04-2.02)	.028	1.32 (.88-1.96)	.177
Adjusted model†				
Runs of PACs	1.47 (1.06-2.04)	.023	1.54 (1.05-2.23)	.028
Age	1.04 (1.03-2.04)	<.001	1.08 (1.06-1.11)	<.001
Male sex	1.41 (1.02-1.96)	.037	1.65 (1.12-2.43)	.011
Previous stroke	1.51 (1.05-2.17)	.026	1.31 (.85-2.03)	.225

Abbreviations: CI, confidence interval; HR, hazard ratio; PAC, premature atrial complex; SSS, Scandinavian Stroke Scale; TIA, transient ischemic attack.

\*Baseline hazard was stratified by SSS groups for the combined endpoint, and by SSS groups and sex for the endpoint of death.

†The model includes only patients with mild and moderate ischemic stroke (SSS > 25) (n = 489), and is adjusted for age, sex, and previous stroke.

runs of PACs, was associated with the risk of AF during the follow-up (Table 3).

**Discussion**

To our knowledge, this is the first cohort study investigating the prevalence and prognostic significance of runs of PACs among ischemic stroke patients in sinus rhythm. In this study, 28% of the patients had runs of PACs, as

assessed by 48-hour CICT. These patients had more severe strokes than those without runs of PACs. In the patients with mild-to-moderate strokes, those with runs of PACs had a worse long-term prognosis, with a higher recurrence of stroke and mortality rate compared with patients without runs of PACs.

With regard to the prevalence of runs of PACs, our findings concur with the findings in a previous study that reported runs of AF of less than 30 seconds among 18%

**Table 3.** Competing risk models showing SHRs of runs of PACs for recurrent ischemic strokes/TIAs and AF in the follow-up, with death as a competing risk

	Recurrent ischemic stroke/TIA*		AF in follow-up†	
	SHR (95% CI)	P	SHR (95% CI)	P
Crude model				
Runs of PACs	1.31 (.81-2.12)	.267	1.44 (.61-3.44)	.406
Adjusted model				
Runs of PACs	1.43 (.88-2.33)	.153	1.24 (.50-3.09)	.649
Age	.99 (.88-2.33)	.470	1.03 (.99-1.07)	.136
Male sex	.90 (.55-1.47)	.671	.68 (.28-1.68)	.401
Previous stroke	2.02 (1.19-3.44)	.010	—	—
Hypertension	—	—	3.16 (1.20-8.35)	.020
Adjusted model‡				
Runs of PACs	1.53 (.93-2.54)	.097	—	—

Abbreviations: AF, atrial fibrillation; CI, confidence interval; PAC, premature atrial complex; SHR, subdistribution HR; SSS, Scandinavian Stroke Scale; TIA, transient ischemic attack.

\*The adjusted models were adjusted for age, sex, and previous strokes.

†The adjusted model was adjusted for age, sex, and hypertension.

‡The model includes only patients with mild and moderate ischemic stroke (SSS > 25) (n = 489), and the analysis was not performed for the endpoint of AF because the sample size was too small.

of patients with a cryptogenic stroke.<sup>17</sup> Studies have also reported runs of PACs in healthy individuals, but the different definitions of PACs and the different monitoring strategies being used make findings in studies difficult to compare.<sup>5,18</sup>

Currently, runs of PACs and frequent PACs are being left untreated, even though they are found to be associated with the risk of AF both among healthy adults and stroke patients.<sup>5-9</sup> This might be explained by the lack of a standard definition for excessive atrial ectopic activity and the fact that its prognostic significance is not clarified. In contrast, the prognostic significance of having AF is well studied, and increased mortality rates in patients with ischemic stroke and AF are frequently reported.<sup>19,20</sup> Moreover, patients with AF tend to have more severe strokes.<sup>2</sup> Similarly, we found that patients with runs of PACs, despite lower rates of diabetes mellitus, hypertension, previous MI, or previous stroke, had more severe strokes and a higher rate of recurrent ischemic stroke/TIAs or death than the patients without runs of PACs. These results may indicate that the mortality risk of patients with runs of PACs is similar to that of patients with AF.

In survival analyses of stroke patients, stroke severity is an important factor. A number of studies reported that stroke severity was an overall predictor of death, although the severity of the stroke had a greater effect on short-term (1-month and 1-year) survival than it did on long-term (5-year and 10-year) survival.<sup>21,22</sup> We studied long-term survival in the present study and stratified the patients according to stroke severity because it is important in a clinical context. We excluded the patients with severe stroke in an adjusted analysis, because it is well known that patients with severe strokes have high mortality risk<sup>23</sup> or suffer severe disabilities, making secondary prevention not clinical as relevant as for those with mild-to-moderate ischemic stroke. This was also the case in the present study, with a mortality rate of 75% within the first year among patients with severe stroke. Therefore, the most informative analyses of the present study were the ones that only include the patients with mild-to-moderate ischemic stroke, as those patients might benefit from further secondary prevention.

In the present study, the combined endpoint was mainly driven by mortality. The association of runs of PACs and the risk of stroke recurrence was not statistically significant; however, there was a trend in all the competing risk analyses. The relationship between frequent PACs and recurrent strokes in stroke patients is only investigated in 1 previous study, in which they found an increased risk of recurrent strokes among patients with frequent PACs.<sup>24</sup> In contrast to the latter study, we considered death as a competing risk in the statistical analysis in the present study, which could explain the incongruent results.

The way in which PACs contribute to an elevated risk of recurrent ischemic strokes/TIAs or death is unclear.

The most likely underlying mechanism is that runs of PACs precede or are a precursor of subclinical paroxysmal AF. Nevertheless, we cannot rule out that the presence of runs of PACs could only be a marker of heart disease and cardiovascular mortality.

In our study, runs of PACs were not associated with the incidence of AF during follow-up. However, the incidence of AF was very likely underestimated because it was registered only in the discharge diagnosis codes of the medical records. Potentially, some patients had silent AF (undiagnosed) or AF diagnosed by their primary care provider. The lack of outpatient monitoring during follow-up is a limitation of the present study. Furthermore, it was not possible to account for structural cardiac abnormalities because results of echocardiography examinations were not available.

The current study has further limitations. It is limited by its retrospective design. The data were collected during routine clinical work, which may have affected the accuracy of the data. Another limitation of the study is missing data. Although there were few incidents of missing baseline data in the registry, the missing data led to fewer patients in the regression analyses. Furthermore, we did not validate the data obtained from the DSR by cross-checking them with patient records, but extensive efforts are made to ensure the validity of the DSR, including regular structured audits and validation of the completeness of registration against county hospital discharge registries. Although there were no patients lost to follow-up, and we adjusted for a wide range of prognostic factors, the possibility that residual confounding could have influenced the results cannot be excluded.

## Conclusions

Runs of PACs were frequent among patients with acute ischemic strokes. In the patients with mild-to-moderate strokes, runs of PACs were independently associated with an increased risk of a recurrent ischemic stroke/TIA or death. It may be considered whether such patients are candidates for prolonged cardiac monitoring to determine the presence of AF. Furthermore, studies are needed to determine whether such patients could benefit from anticoagulant treatment to reduce the risk of recurrent strokes.

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