

Atrial fibrillation characteristics in patients with ischaemic stroke

Jacek Staszewski

Department of Neurology, Military Medical Institute, Warsaw, Poland

Abstract

Background: Atrial fibrillation (AF) is a common arrhythmia and an important risk factor for ischaemic stroke (IS).
Aim: To assess the frequency of AF, including paroxysmal (pAF), persistent (psAF) and permanent AF (pmAF), in patients hospitalised due to IS as well as to establish the natural course of AF and IS prognosis.

Methods: A prospective, non-interventional study of consecutive acute stroke patients with AF with a 6-month follow-up. A favourable stroke outcome was defined when a patient survived or had no disabling stroke during follow-up.

Results: Within 24 months of recruitment, 838 patients were hospitalised due to IS or transient ischaemic attack. Concomitant AF was diagnosed in 200 (24.4%) of these patients. Permanent AF was observed in 108 (54%), pAF in 70 (35%), psAF in 9 (4.5%), and AF of unknown duration in 13 (6.5%) patients. Mean age, demographics and concomitant treatment did not differ significantly among groups. The pAF patients had less often a disabling stroke on admission (81 and 91 vs. 50%, $p < 0.001$) and discharge (55 and 31 vs. 19%, $p < 0.001$) than pmAF and psAF patients, respectively. In-hospital (13 and 9 vs. 3%, $p < 0.001$) and 6-month mortality rates (35 and 40 vs. 14%, $p < 0.001$) were also significantly higher in pmAF and psAF patients than in the pAF group. Lack of chronic anticoagulation tended to be a risk factor for death (OR 2.1, 95% CI 0.8-5.1, $p = 0.09$). In 20 (66%) patients with pAF who experienced recurrence of spontaneous AF during hospitalisation, a successful pharmacological cardioversion was performed, whereas in 10 (34%) patients sinus rhythm was not restored. Restoration of sinus rhythm was a risk factor for unfavourable stroke outcome in the 6-month observation period (OR 2.14; 95% CI 1.07-4.29; $p = 0.03$). During the study 29 (40%) patients with pAF experienced at least one AF recurrence, and 20 (29%) developed psAF. Transformation of psAF to pmAF was observed in 8 (36%) patients. Disabling stroke on admission was a risk factor (OR 4.5, 95% CI 0.9-22.9, $p = 0.05$) for transformation of pAF to pmAF.

Conclusion: Atrial fibrillation was present in 24.4% of acute IS patients. Paroxysmal AF was diagnosed in 35%, pmAF in 54% and psAF in 11% of patients. During follow-up 29% of pAF progressed to psAF and 36% psAF to pmAF. In-hospital and 6-month mortality rates and the number of patients with disabling stroke were significantly lower in pAF than in pmAF and psAF patients. A trend towards unfavourable outcome was observed among patients not receiving chronic anticoagulation.

Key words: atrial fibrillation, ischaemic stroke, incidence, prognosis, antithrombotic treatment

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Introduction

Atrial fibrillation (AF) is a common arrhythmia in clinical practice and one of the major risk factors of ischaemic stroke (IS). It is estimated that AF occurs in about 25% of patients admitted with IS, but the relative contribution of specific forms of AF in this population remains unknown. Natural history of AF in patients after past IS is also less known. Data are also missing for long-term prognosis in patients with acute IS and

persistent AF in whom sinus rhythm recovery was undertaken compared to maintaining appropriate control of ventricular rate.

The aim of this study was to evaluate incidence of AF, including paroxysmal, persistent and permanent AF, in patients admitted to the Department of Neurology due to IS, determination of natural course of these forms of AF, and prognosis for IS during 6-month follow-up.

Address for correspondence:

Jacek Staszewski MD, Klinika Neurologii, Wojskowy Instytut Medyczny, ul. Szaserów 128, 00-909 Warszawa, tel.: +48 607 871 754, e-mail: staszrej@amwaw.edu.pl

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Methods

A prospective, non-interventional study was planned with 6-month follow-up. The analysis involved consecutive patients admitted to the Department of Neurology from 01 Oct. 2003 to 30 Sep. 2005 (24 months) due to IS or transient ischaemic attack (TIA) with AF diagnosed previously or during current hospitalisation. On admission all patients underwent neurological imaging examination (brain CT and/or MR) confirming ischaemic mechanism of cerebral episode (IS or TIA). The AF classification recommended by the European Society of Cardiology was used (2003) [1]. The following forms were distinguished: recurrent, paroxysmal AF with spontaneous termination within up to 7 days, and persistent AF lasting more than 7 days requiring electrical or pharmacological cardioversion for restoration of sinus rhythm. Permanent AF was defined as long-lasting AF in which cardioversion was contraindicated or ineffective. Subjects with first detected AF, in whom arrhythmia duration was established on the basis of clinical symptoms or previous ECG traces, were classified in the respective AF groups. The other study patients with AF of unknown duration (unAF) were included in the persistent AF group. Electrocardiogram was performed in all patients on admission. Patients with paroxysmal AF and unAF underwent ECG monitoring until restoration of sinus rhythm (SR) or diagnosis of persistent AF.

The follow-up visit took place 6 months after the onset of the index cerebral episode and included ECG trace and reporting of possible change of AF form. Five per cent of patients (2 with paroxysmal AF and 8 with permanent AF) were lost to 6-month follow-up; they did not show-up for the scheduled visit or we were unable to contact them or their guardians by phone.

Atrial fibrillation aetiology was determined on the basis of clinical data and transthoracic echocardiography performed earlier or during hospitalisation. Each stage of investigation (on admission, at discharge and at 6th month visit) comprised evaluation of subjects' neurological condition using a modified Rankin functional scale (mRS; 0-6 scores, where 0 = no neurological deficit, 6 = death). Stroke course was found favourable if a cerebral episode caused neither death nor disability (mRS >2 scores) in 6-month follow-up. All patients underwent standard diagnostic and therapeutic procedures in IS as recommended by the European Stroke Initiative [2]. Patients with acute stroke received acetylsalicylic acid (ASA) (100-300 mg/day). No patient was qualified for tissue plasminogen activator administration. For secondary prevention of stroke, patients were recommended to use oral anticoagulant (target INR = 2.5; range 2.0-3.0). In case of contraindications or if regular

INR monitoring was impossible (e.g. due to significant paresis) ASA was added (150-325 mg/day).

Statistical analysis

Statistical analysis was performed with STATISTICA 6.0 software. Results are shown as means \pm SD or counts and percentages. Normal distribution was checked for all quantitative variables using χ^2 or Shapiro-Wilk tests. None of the analysed parameters showed a normal distribution ($p < 0.01$). For quantitative parameters arithmetic mean and standard deviation were calculated. Assessment of differences between analysed groups was performed with Kruskal-Wallis ANOVA. Statistical significance of differences between groups was confirmed using the Student-Newman-Keuls test. Relationships and differences between qualitative variables were analysed using the χ^2 reliability test. Patients' survival was assessed with Kaplan-Meier product-limit survival analysis. Patients lost to follow-up were treated as cut observations. Log-rank test was used to compare survival function. Independent factors adding to change of AF form were identified using multiple logistic regression analysis. Critical significance level was $p = 0.05$. The p values < 0.001 were rounded to 0.001.

Results

During 24-month enrolment a total of 838 patients were hospitalised due to ischaemic cerebral episodes, including 200 (24.4%) subjects with AF. Of this group, 108 (54%) patients had permanent AF, 70 (35%) paroxysmal AF, 9 (4.5%) persistent AF and 13 (6.5%) unAF. Atrial fibrillation was first diagnosed in 11 patients with paroxysmal AF (15% of all subjects with paroxysmal AF) and 19 with permanent AF (18% of all subjects with permanent AF) during current hospitalisation. Together, with individuals with unAF, they comprised 21% (43/200) of all patients with AF.

Mean age and gender distribution as well as AF aetiology were similar in the three analysed AF groups. Patients with permanent AF had significantly more often diabetes mellitus and heart failure compared to patients with paroxysmal AF (Table I). No significant differences of analysed baseline parameters were observed between permanent and persistent AF as well as paroxysmal and persistent AF groups. In patients with permanent AF, mean time to AF diagnosis was 7 ± 4 years (ranging from 1 to 20 years); in the group with paroxysmal AF, 3 ± 3 years (range of 0-12 years); and in patients with persistent AF, 9 ± 3 months (range of 1-12 months).

Frequency of chronic use of anticoagulants and antiarrhythmics (except for V. Williams class I and III drugs, $p < 0.05$) during outpatient follow-up was similar in

groups with paroxysmal and permanent AF. Patients with persistent AF less often than others received anticoagulation and class II antiarrhythmic drugs (Table II).

Analysis of dominant neurological symptoms showed that the paroxysmal AF group significantly more often had TIA and IS with symptoms suggesting disturbance within the posterior cerebral circulation (supplying occipital lobes, cerebral trunk and cerebellum). Patients with permanent and persistent AF significantly more often were disabled on admission and at discharge than patients with paroxysmal AF. Also in-hospital and 6-month mortality rates were significantly higher in these groups (Table III). Course of cerebral ischaemic episodes showed no significant difference with respect to the

analysed parameters between permanent and persistent AF groups.

Mean hospitalisation duration was similar for all study patients and was 12±9 days in permanent AF, and 11±7 days in paroxysmal and persistent AF groups. Difference in survival probability between paroxysmal and permanent or persistent AF tended to increase along with the follow-up duration and was statistically significant ($p < 0.01$) (Figure 1).

Risk of death at 6 months in the permanent AF group was higher than in the paroxysmal group and similar to that in the persistent AF group (OR 3.4, 95% CI 1.3-8.3, $p < 0.01$; OR 1.1, 95% CI 0.7-2.4, $p = 0.6$, respectively). The presence of persistent AF was

Table I. Baseline characteristics of the studied patients

Parameter	Paroxysmal AF	Permanent AF	Persistent AF	p*
Number of patients	70 (35%)	108 (54%)	22 (11%)	–
Age [years]	76±7	77±10	76±6	NS
including:				
<65 years	3 (4%)	9 (8%)	0	–
65-75 years	29 (41%)	34 (31%)	11 (50%)	–
>75 years	38 (54%)	65 (60%)	11 (50%)	NS
Female gender	46 (66%)	70 (65%)	13 (59%)	NS
Atrial fibrillation:				
lone	2 (3%)	1 (1%)	0	–
valvular	9 (13%)	20 (19%)	0	–
organic	58 (83%)	85 (79%)	22 (100%)	NS
Arterial hypertension	64 (93%)	101 (94%)	20 (91%)	NS
Ischaemic heart disease	39 (57%)	73 (68%)	11 (50%)	NS
Heart failure	25 (36%)	65 (61%)	9 (41%)	<0.01
Diabetes mellitus	14 (20%)	43 (40%)	9 (41%)	0.01
Hyperlipidaemia	44 (66%)	48 (51%)	11 (50%)	NS
Hyperthyroidism	9 (13%)	9 (9%)	2 (9%)	NS

*differences between paroxysmal and permanent AF groups

Table II. Frequency of anticoagulants and antiarrhythmics drug use during 6-month follow-up

Parameter	Paroxysmal AF	Permanent AF	Persistent AF	p*
Number of patients	68	94	20	
Antiplatelet agents	36 (53%)	48 (51%)	16 (80%)	<0.05
Anticoagulant agents	32 (47%)	46 (49%)	4 (20%)	<0.05
Antiarrhythmic drug class				
I	5 (7%)	0	0	NS
II	38 (57%)	51 (58%)	6 (30%)	<0.01
III	9 (13%)	3 (3%)	1 (5%)	NS
IV	11 (16%)	14 (16%)	1 (5%)	NS

*differences between persistent and paroxysmal as well as persistent and permanent AF groups

Table III. Comparison of neurological signs and symptoms as well as in-hospital and long-term mortality between the AF groups

Neurological symptoms	Paroxysmal AF	Permanent AF	Persistent AF	p*
Transient ischaemic attack	15 (21%)	7 (6%)	2 (9%)	0.01
Posterior circulation symptoms	16 (23%)	11 (10%)	1 (5%)	0.07
Functional independence on admission	35 (50%)	20 (19%)	2 (9%)	<0.01
Functional independence at discharge	57 (81%)	49 (45%)	13 (59%)	<0.01
In-hospital mortality	2 (3%)	14 (13%)	2 (9%)	<0.01
Six-month mortality	10 (14%)	38 (35%)	9 (40%)	<0.01

*differences between paroxysmal and permanent as well as paroxysmal and persistent AF groups

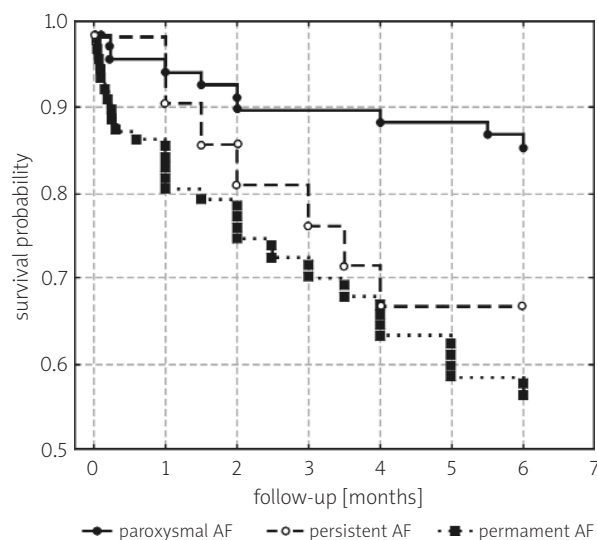


Figure 1. Kaplan-Meier survival curves

associated with a trend towards higher probability of death when compared to paroxysmal AF (OR 1.6, 95% CI 0.8-3.0, $p=0.09$). Causes of deaths were similar for all groups and included: another stroke (50%, including 2 cases of haemorrhagic strokes), infections (25%), pulmonary embolism (10%), myocardial infarction (10%), and progression of heart failure (4%). Of patients who died due to recurrent stroke, concomitant pulmonary oedema was diagnosed in 25% of cases. Multiple regression analysis, taking into account baseline disability and AF type, showed a trend towards higher mortality rate in patients not taking prophylactic anticoagulation (OR 2.1, 95% CI 0.8-5.1, $p=0.09$). No statistically significant effects of any antiarrhythmic drug class on long-term prognosis was found ($p > 0.1$).

During hospitalisation 30 (43%) patients with paroxysmal AF experienced another AF episode which

failed to resolve spontaneously. In 20 (66%) of these patients, SR was restored with pharmacological cardioversion; the other 10 (34%) remained in AF. Taking into account patients' baseline neurological condition, it was shown that SR resolution was associated with statistically significant increase of fatal complication of stroke in 6-month follow-up (OR 2.14; 95% CI 1.07-4.29; $p=0.03$). Deaths in the majority of this group (9/20, 45%) were caused by recurrent stroke and were observed most often within 2 months post cardioversion. Only 5 (55%) of these patients were chronically taking anticoagulation agents after discharge.

During follow-up, 29 (40%) subjects with known paroxysmal AF experienced at least one episode of AF, and 20 (29%) developed persistent AF. The important factor of transformation from paroxysmal to persistent AF, with respect to antiarrhythmic agents used to prevent AF, was patient disability at discharge (OR 4.5, 95% CI 0.9-22.9, $p=0.05$). During the entire follow-up recurrent arrhythmia was not observed in 5 (45%) of 11 patients with confirmed first episode of paroxysmal AF. Diagnosis of permanent AF was confirmed in 36% of patients with persistent AF during the study period.

Discussion

Atrial fibrillation is the most common arrhythmia in patients hospitalised with IS. In the majority of them it is also the direct cause of stroke. The incidence of AF in our patients (24.4%) is slightly higher than data from Western European and American stroke registries (17-24%); however, it is consistent with data from the Warsaw Stroke Registry (26%) conducted from 1991 to 1992 [3-8]. The high percentage of AF in our group was most likely caused by inclusion of patients with paroxysmal AT, who usually were not included in the previous analyses, as well as higher mean patient age which favours AF.

Due to differences in selection of patients in the earlier analyses (e.g. no differentiation between ischaemic and hemorrhagic strokes and exclusion of patients with valvular AF), there are many discrepancies in the reported incidence of individual types of AF in patients with IS. Paroxysmal AF is associated with similar risk of stroke as permanent AF, although it is diagnosed less often probably due to unstable course and diagnostic difficulties [9]. In SPAF I-III studies involving patients with paroxysmal and permanent AF, patients with paroxysmal AF comprised 27% of cases, whereas in the Italian L'Aquila Register – only 6.3% [7, 10]. The low incidence of paroxysmal AF in the latter registry was most likely caused by a higher mean age of the study population (80 years) and exclusion of TIA patients.

The higher incidence of paroxysmal AF in our analysis might be also due to the inclusion of patients with previously unknown AF. Despite this we cannot certainly exclude omission of patients with asymptomatic paroxysmal MP with rare arrhythmic events. Such a type of paroxysmal AF is however associated with a low risk of IS. It is believed that even including Holter ECG monitoring or event-loop recording in the extended diagnostic process in patients with acute stroke without clinical symptoms of arrhythmia allows no more than 5% of previously unknown AF cases to be identified [11]. To our knowledge, no study analysed the incidence of persistent AF in patients with IS. Twenty-one per cent of patients with newly diagnosed AF in our study is consistent with the results of other studies [12]. During a long-term follow-up, 80% of these patients are usually diagnosed with permanent AF, 10% with paroxysmal AF and in the remaining 10% AF does not recur and is found to result from stroke itself [12, 13]. The mechanism triggering AF in such cases remains unclear. Humoral factors are proposed as a potential cause. It was proven that acute cerebral ischaemia leads to sudden release of cortisol and activation of the renin-angiotensin-aldosterone system, and increased aldosterone synthesis may induce an AF episode.

Numerous population and clinical studies have revealed the harmful effects of AF on IS course [14]. However, detailed analysis of influence of individual AF type on prognosis in stroke has not been carried out. Assessment of cerebral episodes in our study group showed that prognosis in patients with acute ischaemic cerebral episodes was dependent on the AF type. Patients with paroxysmal AF had better short-term and long-term prognosis than patients with chronic types of AF. This may be linked to a lower incidence of cardiogenic strokes which typically have worse prognosis than thrombo-atherosclerotic strokes, lower

mean age and lower incidence of comorbidities (heart failure in particular) or more favourable haemodynamic and haemostatic profiles, which most likely determine the course of acute stage of stroke [15, 16].

Failure to use chronic anticoagulation in all patients, who should receive such a treatment, probably unfavourably influenced the prognosis and was independent of AF type. Only every second patient with paroxysmal or permanent AF and every fifth patient with persistent AF were treated with oral anticoagulation. This was partially caused by the presence of contraindications (e.g. extensive infarct area of the brain), inability to regularly control INR and poor compliance in about 30% of patients. It has been shown that oral anticoagulants are significantly more effective than ASA in prevention of cardiogenic stroke (relative risk reduction 60%), which is commonly related to poor prognosis and high mortality rate [17].

Worse long-term prognosis was also observed in patients after restoration of SR during hospitalisation. This was due to recurrent cardiogenic stroke caused in half of patients probably by the lack of anticoagulation. Other factors contributing to increased thrombotic risk in this group cannot be ruled out. Despite AFFIRM trial outcomes, in which maintaining SR was not superior to the rate control strategy (also an adverse trend was observed regarding increased frequency of IS in patients after cardioversion [18]), there are still no guidelines on management of haemodynamically compensated patients with acute stroke. This leads to the necessity of better selection of patients undergoing cardioversion and maybe even postponing or abandoning cardioversion in patients with apparent good tolerance of AF. However, further investigations are required to confirm this hypothesis.

Limitations

The study involved a relatively large number of patients, although conducting an observational study in one site only prevents extrapolation of outcomes to the entire population with IS and AF. Patient count in some of the analysed subgroups was low, which led to less significant results with wider confidence intervals.

Conclusions

Atrial fibrillation was a frequently observed arrhythmia present in one fourth of all admissions for ischaemic cerebral episode. Paroxysmal AF was observed in 35% of these patients, which confirms that this type of AF remains a significant risk factor of ischaemic cerebral episodes. The other patients were

diagnosed with chronic types of AF, in particular permanent AF. During 6-month follow-up arrhythmia turned into persistent AF or permanent AF in 29% of patients with paroxysmal AF and 36% of patients with persistent AF, respectively. Clinical course of ischaemic cerebral episodes in the analysed AF groups varied. Disabling or fatal IS were observed less often in patients with paroxysmal AF than subjects with permanent and persistent AF in both long-term and short-term follow-up. Regardless of AF type, patients not taking chronic anticoagulation therapy were shown to have a tendency to higher long-term mortality.

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Charakterystyka migotania przedsionków u chorych z niedokrwiennym udarem mózgu

Jacek Staszewski

Klinika Neurologii, Wojskowy Instytut Medyczny, Warszawa

Streszczenie

Wstęp: Migotanie przedsionków (ang. *atrial fibrillation*, AF) jest najczęstszą arytmia spotykaną w praktyce klinicznej i jednym z najważniejszych czynników ryzyka niedokrwiennego udaru mózgu (ang. *ischaemic stroke*, IS). Udział poszczególnych postaci AF w tej populacji, ich naturalny przebieg oraz rokowanie nie zostały jednak dotychczas dokładnie określone.

Cel: Ocena częstości występowania AF, w tym nawrotowego napadowego (pxAF), utrwalonego (pmAF) i przetrwałego (psAF) AF wśród chorych hospitalizowanych z powodu IS w naszej klinice, określenie naturalnego przebiegu wymienionych postaci AF oraz rokowania w IS.

Metodyka: Badanie prospektywne, nieinterwencyjne z 6-miesięcznym okresem obserwacji. Do analizy włączono kolejnych chorych hospitalizowanych w naszej klinice między 1 października 2003 a 30 września 2005 r. z powodu IS lub przemijającego incydentu niedokrwiennego (ang. *transient ischaemic attack*, TIA) z rozpoznaniem w przeszłości lub w trakcie obecnej hospitalizacji AF. Korzystano z podziału AF zalecanego przez Europejskie Towarzystwo Kardiologiczne. Pacjenci z AF o nieustalonym czasie trwania byli zaliczani do grupy pmAF. Stan neurologiczny badanych oceniano przy przyjęciu do szpitala, przy wypisie oraz podczas wizyty w 6. mies. w funkcjonalnej skali niesprawności Rankina. Za pomyślny przebieg udaru uznawano incydent mózgowy, który w okresie 6-miesięcznej obserwacji nie prowadził do zgonu lub niesamodzielnosci.

Wyniki: Przez 24 mies. hospitalizowano łącznie 838 chorych z IS lub TIA, z tego u 200 (24,4%) stwierdzono towarzyszące AF. W tej grupie rozpoznanie pmAF postawiono u 108 (54%) badanych, pxAF i psAF u odpowiednio 70 (35%) i 9 (4,5%) chorych, AF o nieustalonym czasie trwania u kolejnych 13 (6,5%) chorych. Średnia wieku, rozkład płci oraz etiologia AF nie różniły się istotnie między analizowanymi grupami. Nie obserwowano istotnych różnic między grupami pxAF i pmAF w częstości stosowania leków przeciwzakrzepowych oraz antyarytmicznych (poza częstszym stosowaniem leków klasy I i III w pxAF) w trakcie obserwacji ambulatoryjnej. Badani z psAF rzadziej niż pozostali pacjenci otrzymywali leczenie antykoagulacyjne oraz antyarytmiczne klasy II. Chorzy z pmAF i psAF istotnie częściej niż z pxAF byli niesamodzielnymi przy przyjęciu (odpowiednio 81 i 91 vs 50%, $p < 0,001$) i wypisie ze szpitala (55 i 31 vs 19%, $p < 0,001$). Również śmiertelność wewnątrzszpitalna (13 i 9 vs 3%, $p < 0,001$) i 6-miesięczna (35 i 40 vs 14%, $p < 0,001$) były znacząco wyższe w pmAF i psAF niż w pxAF. W analizie wieloczynnikowej, niezależnie od postaci AF, stwierdzono trend do gorszego rokowania odległego u chorych niestosujących przewlekłego leczenia antykoagulacyjnego (OR 2,1; 95% CI 0,8–5,1; $p=0,09$). Leki antyarytmiczne nie wpływały istotnie na rokowanie. U 20 (66%) chorych z pxAF, u których wystąpił nieustępujący samoistnie incydent AF w trakcie hospitalizacji, przywrócono rytm zatokowy (RZ) przy zastosowaniu farmakologicznej kardiowersji, u kolejnych 10 (34%) nie uzyskano trwałego powrotu RZ. Przywrócenie RZ wiązało się ze wzrostem ryzyka niepomyślnego zajścia (udar) w obserwacji 6-miesięcznej (OR 2,14; 95% CI 1,07–4,29; $p=0,03$). W trakcie badania u 29 (40%) badanych z rozpoznaniem pxAF wystąpił co najmniej jeden incydent AF, u 20 (29%) odnotowano zmianę postaci arytmii w psAF, u 8 (36%) chorych z psAF postawiono rozpoznanie pmAF. Czynnikiem ryzyka transformacji pxAF w psAF była niesamodzielnosc przy wypisie ze szpitala (OR 4,5; 95% CI 0,9–22,9; $p=0,05$).

Wnioski: Wśród 24,4% chorych hospitalizowanych z powodu mózgowego incydentu niedokrwiennego stwierdzono współistniejące AF. U 35% obserwowano pxAF, u pozostałych badanych rozpoznawano przewlekłe formy arytmii, głównie pmAF (54%). W trakcie 6-miesięcznej obserwacji u 29% chorych z pxAF i 36% z psAF nastąpiła zmiana postaci arytmii w odpowiednio psAF lub pmAF. Przebieg kliniczny mózgowych incydentów niedokrwiennych w analizowanych grupach chorych z AF był odmienny. U chorych z pxAF rzadziej niż u pozostałych stwierdzano występowanie udarów niedokrwiennych mózgu prowadzących do utraty samodzielności lub do zgonu, zarówno w obserwacji krótkoterminowej, jak i odległej. Niezależnie od postaci AF, obserwowano trend do niekorzystnego rokowania odległego wśród chorych nieotrzymujących przewlekłego leczenia antykoagulacyjnego.

Słowa kluczowe: migotanie przedsionków, udar mózgu, częstość występowania, rokowanie, leczenie przeciwzakrzepowe

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Adres do korespondencji:

dr n. med. Jacek Staszewski, Klinika Neurologii, Wojskowy Instytut Medyczny, ul. Szaserów 128, 00-909 Warszawa, tel.: +48 607 871 754, e-mail: staszrej@amwaw.edu.pl

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