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Atrial fibrillation and stroke – Coexistence and attitude to preventive therapy on the basis of Szczecin and Szczecin region patients

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ABSTRACT

Atrial fibrillation (AF) is an independent factor increasing the risk of an ischemic stroke (IS) fivefold. The objective of the study was to evaluate the frequency of coexistence of non-valvular AF and IS during the acute stroke and to analyze the attitude of AF patients to treatment.

The study included 3712 successive patients presenting either an IS or a transient ischemic attack.

The analysis revealed a significant increase in the rate of patients with AF and IS in the years 2010–2013 (31.9%) compared with 2002–2005 (20.2%). A rise in the proportion of AF and IS patients was recorded over the course of consecutive years in group II. The proportion of newly detected AF cases during hospital stay differed significantly between the groups (16.9% vs. 31.9%). Group I and II patients differed essentially with regards to hypertension incidence and female rates. Antiplatelet medications or OACs were taken by a significantly greater number of AF patients in group II. Low number of therapeutic levels of INR was recorded in both groups.

IS and AF coexist more frequently than indicated by previous assessments and demographic data from other countries. Increase in the number of IS and AF patients may result from higher detectability of AF and older age of patients affected with stroke, women in particular. Despite a well grounded knowledge about the benefits of OACs use in the prophylaxis of thrombotic-embolic events in AF patients, they are rarely used. A surprisingly low proportion of patients taking OACs reaches a therapeutic INR level.

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Atrial fibrillation (AF) is the most frequent atrial tachyarrhythmia and one of the essential modifiable ischemic stroke (IS) risk factors [1]. AF incidence increases with age. Over the last 50 years, due to the population aging the number of AF patients doubled. AF affects 2–3 patients out of 1000 patients aged 25–5; 30–40 patients out of 1000 patients aged 55–64, and 50–90 out of 1000 patients aged 62–90. It is estimated that the disease affects approximately 10% of all past the age of 80 [2]. Currently, there are circa 6 million Europeans suffering from the disease [3].

With regards to atrial fibrillation etiology, AF is divided into spontaneous (idiopathic) AF and secondary AF, further subdivided into valvular and non-valvular [4]. Non-valvular AF accounts for ca. 50% of all AF cases [5].

AF as a condition predisposing to the development of arterial embolism seems of particular importance to neurologists, since as much as 70–90% of all cardiogenic embolisms affect cerebral arteries [6,7]. AF prevalence places it at the forefront of cardiogenic causes of stroke [8,9]. According to the most widely cited studies from Framingham, AF is independently associated with a five-fold elevated risk for stroke [9,10]. AF is diagnosed in 6–26% of IS patients, 8–36% of stroke patients >80 years of age [11–15]. In a study involving the Warsaw city population, AF affected 22.8% of stroke patients hospitalized between 1991 and 1992, and 25% of those hospitalized in 2005 [16]. In patients above 80, AF is considered the strongest single IS risk factor [17]. Annual incidence of stroke in a general population of AF patients is 5% [18]. In Poland, it is markedly higher than in the Western European countries [18].

Prognosis in IS in the context of cardiogenic embolism is typically more serious than in stroke of thrombotic origins. Stroke developing in AF patients features high rate of recurrence, more severe course, and higher rate of early mortality [19,20]. Embolism-caused strokes are more often to blame for permanent post-stroke disability than thrombotic or lacunar ones [19–23].

Because of the relationship between AF and IS, the worldwide interest in the issue and ongoing search for the measures to prevent embolic complications in AF patients is not surprising.

Subject literature provides numerous research findings in favor of the claim that oral anticoagulant (OAC) prophylaxis in AF patients is more beneficial than antiplatelet preparation use [24]. It has been demonstrated that compared with acetylsalicylic acid (ASA), it significantly lowers the risk of IS in AF patients, only slightly increasing the total risk of a serious bleeding [18,25]. Despite perfectly substantiated advantages of OAC prophylaxis, its limited application is still common.

Taking into consideration the above mentioned wide discrepancies regarding AF and IS coexistence in epidemiological analyses and single findings concerning the issue in Poland, we set off to evaluate the incidence of coexistence of non-valvular AF and IS, including the first detected AF (fd AF) in the acute stroke, and to analyze the attitude of AF patients to OAC therapy on the basis of the Szczecin and Szczecin region patients, assuming that obtained results would be representative of the overall situation in the country. Furthermore, we decided to monitor both aspects, particularly the latter, in two time periods: 2002–2005 and 2010–2013. The former period corresponds to the early years following the introduction of the National Program for Stroke Prevention and Treatment in Poland (year 2000), guidelines on the management of acute stroke, and the basis for secondary stroke prevention. The latter refers to the time at which the effects of educational activities regarding the rules of stroke prevention should be expected.

1. Materials and methods

The study included 3712 patients with either an IS or a transient ischemic attack (TIA) hospitalized in the Neurological Department of the Pomeranian Medical University (PMU) in Szczecin between 2002 and 2005 (1525 consecutive patients – group I) and between 2010 and 2013 (2187 consecutive patients – group II). The analysis of group I patients was conducted retrospectively, whereas that of group II was prospective.

All patients were evaluated with the application of a specially designed questionnaire listing personal data, data regarding coexisting conditions, including but not limited to stroke risk factors, and current treatment, in particular any antiaggregants and OACs. The use of antiaggregants involved the taking of ASA, ticlopidine and/or clopidogrel; the use of OACs – acenocoumarol or warfarin. Information was obtained directly from the patients and their families and from the medical records submitted.

All patients underwent neurological examination, a standard 12-lead electrocardiogram (ECG) and, if necessary, a 24-h Holter monitoring, Doppler ultrasound of carotid arteries, and routine laboratory analyses. In addition, the fd AF patients had an echocardiography performed. Computed tomography (CT) every time was conducted at admission.

The ''established'' AF was defined as a paroxysmal, persistent or permanent AF diagnosed on the basis of repeated 12-lead ECGs and/or the 24-h continuous Holter monitoring prior to stroke. Fd AF was defined as an AF diagnosed pursuant to an elective or symptom-dependent standard 12-lead ECG and/or 24-h Holter monitoring (at admission or during hospital stay) in patients with no prior AF history.

The grounds for diagnosing arterial hypertension and type 2 diabetes were patient history, medical records and drugs used. Newly detected arterial hypertension was diagnosed when at repeated tests the systolic blood pressure (SBP) was ≥140 mmHg and/or the diastolic blood pressure (DBP) was ≥90 mmHg [26]. Newly diagnosed diabetes was determined by the level of fasting blood glucose after a minimum of 2 test results ≥126 mg/dl or glucose level ≥200 mg/dl marked at any time during the day. An alternative criterion for diagnosing diabetes was a positive result of a glucose tolerance test (blood glucose ≥200 mg/dl 2 h after oral administration of 75 mg of glucose) [27].

Valvular and secondary AF patients were excluded from the study. The exclusion criteria included: hemodynamic significant mitral valve stenosis or an artificial valve and a passing AF induced by a reversible clinical condition (ionic imbalance, myocardial infarction, thyreotoxicosis, pulmonary embolism).

2. Statistical analysis

The majority of the distributions of the analyzed continuous variables was significantly different from the normal distribution pattern (Shapiro–Wilk test); thus, analyses were performed with the application of non-parametric tests. To assess the significance of the differences in variables between the two examined patient groups the following tests were conducted: the Kruskal–Wallis test, the Mann–Whitney U test, and the chi-square test. Logical regression was applied to the multivariate analysis of the odds ratio (OR) at 95% confidence interval (95% CI). Statistical significance was set at $p < 0.05$. Calculations were performed with the use of STATISTICA ver. 10.1.

3. Results

The analysis revealed a significant increase in the rate of patients with AF and IS in the years 2010–2103 compared with 2002–2005 (group II – 31.9%, group I – 20.2% respectively, $p = 0.0003$). No statistically significant difference was observed in the proportion of patients with paroxysmal and permanent AF between the groups (group I: 39% paroxysmal, 62% permanent, group II: 34% paroxysmal, 67% permanent, $p = 0.1588$). A rise in the proportion of AF and IS patients was recorded over the course of consecutive years in group II. A significant increase was recorded between the year 2010 and 2011 ($p = 0.0031$). In the year 2012, the proportion was similar to that of the year before. In 2013, in turn, it was higher than in 2012. The most marked difference was observed between the years 2010 and 2013 ($p = 0.0004$). However, there were no differences between the rate of patients with AF and TIA in consecutive years in group II (Fig. 1).

Demographic data of AF and IS patients in both groups are presented in Table 1. It shows that the patients differed essentially with regards to arterial hypertension incidence and female rates.

Based on Table 2 data, the proportion of the newly detected AF cases during hospitalization due to a first-time stroke did not differ significantly over following years in group II. However, it was significantly lower in group I (16.9%). The number of AF patients taking antiplatelets or OACs was significantly higher in group II. Still, in spite of extensive knowledge about arrhythmia, prior to stroke OACs were used by a relatively small proportion of patients in both groups: 10.2 and 18.3% respectively (group I vs. II, $p = 0.0066$); antiaggregants were taken by 36.7 and 46.6%, respectively (group I vs. II, $p = 0.0071$).

Looking at the INR values in patients with AF established prior to stroke, we found that the proportion of patients with the ratio of 2.0–3.0 or >3.0 (which meant they were taking a drug) was significantly low (Fig. 2).

Table 1 – Demographic statistics of AF patients from group I and II.

	Group I	Group II	p Value
Patients number	316 (20.2%[a])	569 (26.01%[a])	0.0003
Age	46–93 years median 76 (SD ± 9.1)	40–97 years median 79 (SD ± 9.6)	0.7638
Sex (female)	57.9%	67.5%	0.0047
Hypertension	74.7%	83.3%	0.0024
Diabetes mellitus	33.2%	29.5%	0.0931
Vascular disease[b]	22.8%	22.3%	0.8739
Stroke/TIA in history	33.2%	28.5%	0.1396

[a] Per cent of whole group.
[b] Peripheral artery disease, carotid artery disease, myocardial infarct.

Table 2 – First detected AF in first ever stroke patients – comparison between consecutive years of group II (n = 439 individuals).

2010	29.3%[a]	
		$p = 0.2051$
2011	37.6%	
		$p = 0.1031$
2012	28.2%	
		$p = 0.5155$
2013	32.5%	

4. Discussion

IS and AF coexistence estimate is highly varied and, depending on the source, it may affect between 6 and over 30% of IS patients [12,14,16,28]. In a multicenter study evaluating factors influencing delayed onset of thrombotic treatment in IS conducted in the Central and Eastern European countries, including Poland, AF was recorded in 25% of patients [29]. Other studies involving a Polish group of IS patients revealed that AF affected between 23.6 and 30.1% of patients [30–32]. In a study of Caucasian population evaluating the dependency between renal failure

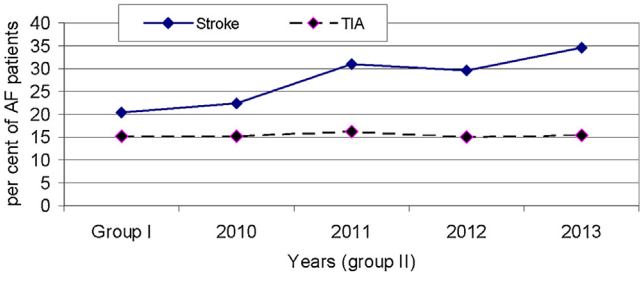

Fig. 1 – Per cent of AF patients in regard to whole group I and consecutive years of group II.

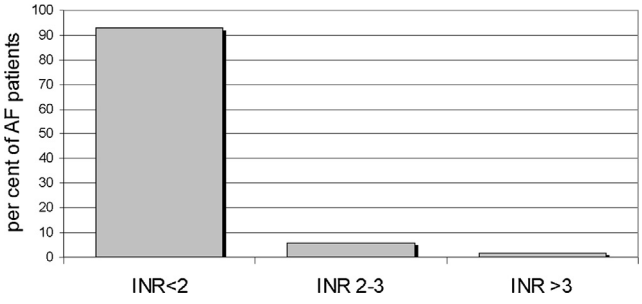

Fig. 2 – International Normalized Ratio (INR) in group II patients with AF history prior to stroke.

and thrombotic treatment outcomes in IS patients, AF affected as much as 36.4% of study participants [33].

Our findings indicate a significant increase in the number of patients with AF and IS in the years 2010–2013 compared with 2002–2005. The proportion of patients in 2013 was as high as 35%. Nevertheless, we are unable to state what is the explicit cause of such significant increase in the ratio of AF and IS patients over the last years. Several factors might have contributed to this result. Above all, a rise in AF detectability both preceding and during the hospital stay. Furthermore, group II patients were older (though, not significantly) and thus they more often had arterial hypertension than group I patients (perhaps, they were more often diagnosed with one). Women with a higher risk of AF-associated stroke predominated group II [34]. However, no differences were found between the rate of patients with paroxysmal and permanent AF and TIA between the groups or in group II over the consecutive years. Presumably, such a low, fixed proportion of AF and TIA patients is consequential to permanent underestimation of coexistence of both pathologies since TIA patients' hospital stay is typically short, which often does not allow for passing AF episodes to be identified.

Due to a frequently asymptomatic course of AF, stroke happens to be the first complication of the arrhythmia [35]. It has been demonstrated that the longer the time of electrocardiographic monitoring of patients in the acute IS phase, the better the chance of detecting AF. The ratio of fd AF patients in the acute IS phase rises from just a few percent [35–39] up to more than 30% [40–42]. Gladstone et al. [43] proved that a prolonged ECG monitoring (up to 30 days) in patients after stroke/TIA found initially to be cryptogenic, increases the detectability of paroxysmal AF fivefold compared to standard monitoring. This confirms the need to introduce an extended ECG monitoring in order to properly establish etiology and implement suitable secondary preventive measures [44,45].

In our study, the proportion of fd AF in the years 2010–2013 reached 37.6% (year 2011). This result is based on a routine 24-h Holter monitoring. The above indicates that a globally significant increase in IS and AF coexistence in our patients in the years 2010–2013, may be, at least partially, attributed to higher AF detectability at stroke.

New guidelines considerably extended the range of patients that should be administered a long-term OAC therapy. Only a male under the age of 64 with the so-called isolated, focal, paroxysmal AF and no additional risk factors of developing thrombotic-embolic incidents, may renounce antithrombotic treatment [46–48], although this may be subject to further considerations due to dangerous effects of any potential stroke.

Studies conducted more than 10 years ago demonstrated that in 2002 56% of Americans with AF took OACs [49]. A similar Spanish comparison showed that the ratio of patients taking OACs was almost 30% and antiaggregants – 46%. Nevertheless, we need to stress that despite greater awareness of AF-induced thrombo-embolic risks, the proportion of patients taking OAC is still not optimal. Even findings from the year 2013 indicate that it is ca. 50%, or below [46,50].

The number of AF patients in our study taking antiplatelets or OACs was significantly higher in group II, but despite the fact that arrhythmia was known to be one of the stroke risk factors, OACs were used by a relatively small proportion of patients in both groups prior to stroke: 10.2 and 18.3% respectively. The proportion is at least two- or even 3-times lower than in other comparisons [44,49,50]. If we assumed that AF patients using antiaggregants profited to some extent, the proportion of such patients would still prove insufficient, as the numbers were 36.7% of the patients in group I and 46.6% of the patients in group II.

The underrated issue here is the efficacy of the drugs administered measured by the therapeutic index. Research shows that at most half of the patients taking OACs achieves a therapeutic value of INR (it is possible that it is a mere 20% of the patients) [42]. Considering INR values established prior to stroke in our AF patients admitted to the Department due to stroke, the proportion of patients with a 2.0–3.0 index value or >3.0 (which meant they were taking a drug) was significantly low (barely 9%). This result is particularly striking when compared with the above cited estimates from other studies, where a half of AF patients receiving treatment represented the therapeutic range of OACs. It is largely attributed to the difficulties in maintaining INR in the narrow therapeutic window. Even in patients treated with OACs and attaining INR value of 2.0–3.0 at testing, the total therapeutic time most probably does not exceed 50% of the therapy period [42,46]. In the light of these data, the meaning of our result (9% of the patients) becomes even more negative.

An alternative to VKA and, presumably, the future in IS prevention in AF patients, are novel OACs featuring stable pharmacokinetics, lack of major interactions with other drugs or foods influencing the activity of P450 cytochrome enzymes and, what is essential, not requiring the monitoring of circulation system parameters. Said drugs are becoming more and more widely used in Poland.

Above-described considerations on the AF and stroke, regarding the pathogenesis and treatment of cerebro-vascular events, justify need creating close cooperation with cardiologic teams in searching for AF in every patient with embolic stroke of uncertain source (ESUS).

5. Conclusions

1 Ischemic stroke and atrial fibrillation in the study population coexist more often than indicated by previous estimates and demographic data from other countries.
2 Amongst the causes of the increase in the number of patients with stroke and atrial fibrillation may be higher detectability of atrial fibrillation preceding and, most importantly, during hospital stay, and older age of patients affected with a stroke, women in particular.
3 Despite well substantiated knowledge about the benefits of antithrombotic drug use in the prevention of thromboembolic events in patients with atrial fibrillation, they are used rarely. In addition, a surprisingly low proportion of patients taking antithrombotic drugs reaches the target INR level.

Conflict of interest

The authors declare no financial or other conflict of interests.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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