# Risk factors for ischemic stroke in patients with non-valvular atrial fibrillation and therapeutic international normalized ratio range

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## Abstract

**Introduction:** Atrial fibrillation (AF) is the most common cause of ischemic stroke (IS). Atrial fibrillation patients are recommended to use oral anticoagulants (OACs) as part of prevention against IS. However, despite having a therapeutic intensity of OAC therapy, IS can still occur in such patients. The aim of our study was to examine the configuration of IS risk factors in patients with non-valvular atrial fibrillation (NVAF) and within the therapeutic INR range (TINR).

**Material and methods:** Our retrospective study involved 1835 patients with a recent IS. The experimental group consisted of 154 patients with acute IS, NVAF and TINR. The control group consisted of 1681 patients with acute IS but without AF.

**Results:** Patients with IS, NVAF and TINR were significantly older and more often female than patients with IS without NVAF ($p < 0.001$ and $p < 0.001$, respectively). In these patients, diabetes mellitus, dyslipidemia, hypertension, coronary heart disease, smoking and previous IS were significantly more frequent than in the patients with IS without NVAF ($p = 0.036$, $p = 0.002$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.003$). Based on a univariable and multivariable logistic regression model, we found that in the group of patients who suffered a stroke despite TINR compared to patients with IS without AF there were more smokers (OR = 20.337; OR = 147.589) and patients with previous stroke (OR = 6.556; OR = 11.094), hypertension (OR = 3.75; OR = 2.75) and dyslipidemia (OR = 2.318; OR = 2.294).

**Conclusions:** The group of patients with NVAF and TINR is significantly more burdened by other independent common risk factors for stroke.

**Key words:** atrial fibrillation, ischemic stroke, therapeutic INR.

## Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia. Patients suffering from this condition may develop neurological deficiencies from an embolism or from hemodynamic disorders associated with the heart rhythm itself. AF predisposes to an increased risk of ischemic stroke (IS) by means of transfer of embolic material from the left atrium of the heart to the cerebral vessels [1]. In view of the above, AF patients are recommended to use oral anticoagulants (OACs) as part of secondary prevention against IS, such as vitamin K antagonists and new oral anticoagulants (NOACs). Anticoagulation reduced the risk of stroke from

12% to 4% per year [2, 3]. An interesting phenomenon and an important therapeutic problem is the occurrence of IS in patients with non-valvular atrial fibrillation (NVAF) and in the therapeutic INR range (TINR). With little information available in available literature regarding this problem, the aim of this study was to examine the configuration of IS risk factors in patients with NVAF and TINR.

## Material and methods

Our retrospective study involved 1835 patients with a recent IS, hospitalized at the Department of Neurology, Pomeranian Medical University in Szczecin between January 2011 and December 2014. Patients were divided into two groups. The experimental group consisted of 154 patients (100 women and 54 men) with acute IS, NVAF and TINR. The control group consisted of 1681 patients (855 women and 826 men) with acute IS but without concurrent AF.

Atrial fibrillation was diagnosed based on information from a medical history or electrocardiographic results on admission or during hospitalization. Valvular heart diseases which were used as exclusion criterion from this study were identified based on the patient's history or echocardiographic tests during hospitalization. International normalized ratio was established at admission for each patient who received warfarin or acenocoumarol. In accordance with European guidelines for pharmacotherapy of AF, the recommended INR is from 2.0 to 3.0 for patients with NVAF [4]. Ischemic stroke was defined as sudden onset of a non-convulsive, focal neurological deficit persisting for more than 24 h by means of brain imaging (computed tomography (CT) and/or magnetic resonance imaging (MRI)). Each type of ischemic stroke, both cardioembolic and non-cardioembolic, including lacunar, atherothrombotic and various types, were included in the study. We collected data on the most common risk factors for IS from all patients. Written informed consent was obtained from each patient enrolled in the study. The Pomeranian Medical University Ethics Committee approved the study protocol, which conformed to the ethical guidelines of the Declaration of Helsinki.

Definitions for risk factors:

1. Atrial fibrillation was defined as the absence of P waves in ECG, with the isoelectric line being replaced by irregular high-frequency oscillations (f waves), and wholly irregular ventricular response; this was based on ECG results during admission or in previous medical reports [5].
2. Diabetes mellitus type 2 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 measured 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) [6].
3. Dyslipidemia (serum cholesterol concentration > 190 mg/dl, low-density lipoprotein (LDL) cholesterol > 115 mg/dl, serum triglyceride concentration > 150 mg/dl and high-density lipoprotein (HDL) cholesterol < 40 mg/dl in males and < 45 mg/dl in females) [7].
4. Hypertension was diagnosed when in repeated tests the systolic blood pressure (SBP) was ≥ 140 mm Hg and/or the diastolic blood pressure (DBP) was ≥ 90 mm Hg [8].
5. Coronary heart disease was determined by previous history of angina pectoris, myocardial infarction, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty.
6. Internal carotid artery hemodynamically significant stenosis was defined, with variation from study to study, ranging in degrees of stenosis from 50% to 70% and greater [9, 10].
7. Peripheral arterial disease includes previous history of intermittent claudication, arterial thrombosis, and percutaneous or surgical intervention in the thoracic, abdominal aorta, or lower extremity vessels.
8. Cigarette smoking was defined as current smoking of any number of cigarettes.
9. Previous stroke was considered to be present if the medical charts included a stroke diagnosis or if the individual, a caregiver, or a relative reported the diagnosis and it was found to be credible based on supporting information from medical charts.

### Statistical analysis

The statistical null hypothesis was: there are no differences in risk factors between IS patients with NVAF with TINR and IS patients without AF. The alternative hypothesis was: there are significant differences in risk factors between IS patients with NVAF and TINR and IS patients without AF.

In order to compare characteristics of NVAF and TINR stroke patients with patients without AF, the Mann-Whitney *U* test for quantitative data was used. For qualitative data, Fisher's exact test was used. Multiple logistic regression was calculated for assessing the odds ratio of independent risk factors for stroke in IS patients with AF and TINR compared to patients without AF ($p < 0.05$ was considered to indicate statistical significance). All calculations were performed in R statistical environment (R Version 3.4.4 2018-03-15).

## Results

### Comparison of risk factors for ischemic stroke in patients with non-valvular atrial fibrillation and therapeutic INR range and patients with ischemic stroke without concurrent atrial fibrillation

A case comparison is presented in Table I. Older age, female gender, diabetes mellitus, dyslipidemia, hypertension, coronary heart disease, cigarette smoking and history of ischemic stroke were significantly more frequent in patients with concurrent NVAF and TINR than in patients without AF ($p < 0.001$, $p < 0.001$, $p = 0.036$, $p = 0.002$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.003$). Interestingly, significant ICA stenosis/occlusion was only slightly more frequent in the group of patients without AF ($p = 0.03$).

### Analysis of risk factors of ischemic stroke in patients with non-valvular atrial fibrillation who suffered a stroke despite TINR compared to patients without AF

Based on a univariable and multivariable logistic regression model, we found that in the group of patients who suffered a stroke despite TINR compared to patients with IS without AF there were more smokers (OR = 20.337; OR = 147.589) and patients with previous stroke (OR = 6.556; OR = 11.094), hypertension (OR = 3.75; OR = 2.75) and dyslipidemia (OR = 2.318; OR = 2.294) (Table II).

## Discussion

In this study we confirmed that in addition to the embolic factor associated with AF, patients with TINR were significantly more likely to have other risk factors, including those conducive to thrombotic and thromboembolic mechanisms. Therefore, in the above-mentioned group of patients the risk of developing IS was high even when the INR values remained in the therapeutic range. This seems to confirm the results of a study conducted by Evans *et al.* [11] in which a group of patients with IS and concurrent AF were subjected to a 2-year follow-up. The patients had been treated with warfarin. It was observed that the frequency of lacunar stroke recurrence was higher than that of cardioembolic stroke. According to our analysis, patients with IS, NVAF and TINR were significantly older and mostly female ($p < 0.001$ and $p < 0.001$, respectively). In these patients, type 2 diabetes, dyslipidemia, hypertension, coronary heart disease, smoking and previous IS were significantly more frequent than in the patients with IS without AF ($p = 0.036$, $p = 0.002$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.003$). TINR in this group of patients did not reduce the risk of IS. Based on a univariable and multivariable logistic regression model, we found that in the group of patients who suffered a stroke despite TINR compared to patients with IS without AF there were more smokers (OR = 20.337; OR = 147.589) and patients with previous stroke (OR = 6.556; OR = 11.094), hypertension (OR = 3.75; OR = 2.75) and dyslipidemia (OR = 2.318; OR = 2.294). It should be emphasized that among patients with ICA, significant stenosis/occlusion only slightly predominated in the group without AF, which means that in many patients with AF, ICA and stenosis/occlusion coexist as an important risk factor for

**Table I.** Characteristics of patients with ischemic stroke and non-valvular atrial fibrillation as well as therapeutic INR and patients with ischemic stroke without atrial fibrillation

| Parameter | TINR ($n$ = 154) | AF– ($n$ = 1681) | $P$-value |
|---|---|---|---|
| Age | 77.6 ±10.4 | 69.8 ±12.5 | < 0.001 |
| Female, *n* (%) | 100 (64.9) | 855 (50.9) | < 0.001 |
| Comorbidities, *n* (%): | | | |
| Diabetes mellitus | 59 (38.3) | 514 (30.6) | 0.036 |
| Dyslipidemia | 81 (52.6) | 680 (40.5) | 0.002 |
| Hypertension | 143 (92.9) | 1243 (73.9) | < 0.001 |
| ICA significant, *n* (%): | | | |
| Stenosis/occlusion | 13 (8.1) | 250 (14.8) | 0.03 |
| Coronary heart disease | 92 (59.7) | 705 (41.9) | < 0.001 |
| Peripheral arterial disease | 14 (9.1) | 162 (9.6) | 0.86 |
| Smoking | 101 (65.6) | 883 (52.5) | < 0.001 |
| Previous stroke, *n* (%) | 92 (59.7) | 733 (43.7) | 0.003 |

*ICA – internal carotid artery.*

**Table II.** Analysis of risk factors of ischemic stroke in patients with non-valvular atrial fibrillation, who suffered a stroke despite TINR compared to patients without AF (multivariate logistic regression)

| Factors | Univariable logistic regression models | | | Multivariable logistic regression model* | | |
|---|---|---|---|---|---|---|
| | OR | CI | *P*-value | OR | CI | *P*-value |
| Age | 1.058 | 1.041–1.075 | < 0.01 | 1.113 | 1.084–1.145 | < 0.01 |
| Hypertension: | | | | | | |
| Yes | 3.75 | 2.1–7.432 | <0.01 | 2.751 | 1.263–6.65 | 0.016 |
| No | 1.0 | – | – | 1.0 | – | – |
| Smoking: | | | | | | |
| Yes | 20.337 | 13.618–31.143 | < 0.01 | 147.589 | 74.213–316.588 | < 0.01 |
| No | 1.0 | – | – | 1.0 | – | – |
| Previous stroke: | | | | | | |
| Yes | 6.556 | 4.621–9.359 | < 0.01 | 11.094 | 6.355–20.096 | < 0.01 |
| No | 1.0 | – | – | 1.0 | – | – |
| Dyslipidemia: | | | | | | |
| Yes | 2.318 | 1.649–3.278 | < 0.01 | 2.294 | 1.369–3.896 | < 0.01 |
| No | 1.0 | – | – | 1.0 | – | – |
| ICA significant stenosis/occlusion: | | | | | | |
| Yes | 0.491 | 0.261–0.85 | 0.017 | 0.418 | 0.188–0.863 | 0.024 |
| No | 1.0 | – | – | 1.0 | – | – |
| Gender: | | | | | | |
| Female | 1.0 | – | – | 1.0 | – | – |
| Male | 0.583 | 0.408–0.824 | < 0.01 | 0.366 | 0.206–0.64 | < 0.01 |
| Diabetes mellitus: | | | | | | |
| Yes | 1.306 | 0.917–1.845 | 0.134 | 1.081 | 0.641–1.809 | 0.768 |
| No | 1.0 | – | – | 1.0 | – | – |
| Coronary heart disease: | | | | | | |
| Yes | 1.945 | 1.383–2.751 | < 0.01 | 1.864 | 1.112–3.164 | 0.019 |
| No | 1.0 | – | – | 1.0 | – | – |

**Full adjusted model; Independent variables: age; hypertension (yes/no); smoking (yes/no); previous stroke (yes/no); dyslipidemia (yes/no); ICA significant stenosis/occlusion; sex (F/M); diabetes mellitus (yes/no); coronary heart disease (yes/no). ICA – internal carotid artery.*

stroke which requires different treatment than AF. On one hand, a significant symptomatic stenosis of the artery favors small embolisms already in the extra-cranial section of the artery, and on the other hand it can be a direct cause of a stroke in the hypoperfusion mechanism associated with hemodynamic disturbances resulting from AF. It may also lead to a stroke independently in a thromboembolic mechanism (arterio-arterial). An attempt to combine pharmacological management in secondary stroke prevention in patients with AF (recommended anticoagulant) and that used for ICA stenosis (antiaggregant) would significantly increase the risk of intracranial hemorrhagic complications.

In 2010, the results of the INTERSTROKE survey were announced. In this study, the authors observed that hypertension, smoking, obesity, diet and lack of physical activity are the most important modifiable risk factors for stroke with both ischemic and hemorrhagic etiology. They cause that the risk of stroke is 80%. Including the next five factors – diabetes, alcohol abuse, psychosocial factors, heart disease and apolipoprotein B to A1 ratio – risk of stroke increases to 90%. It is also interesting to compare the risk factors assessed in the INTERSTROKE and INTERHEART trials. The risk factors responsible for 90% of the risk of myocardial infarction and stroke are the same. The differ-

ences concern only their impact strength. While in stroke the most important risk factor is hypertension, in the case of myocardial infarction it is lipid disorders. Patients with stroke are less likely to smoke, have less alcohol abuse and rarely have diabetes [12, 13].

Hypertension is not only one of the most frequent causes of first stroke, but also increases the risk of recurrent stroke in patients who have had this episode in the past, and the risk of morbidity and mortality from cardiovascular causes [14]. Treatment of hypertension significantly reduces the risk of vascular death and general mortality, and the reduction of risk depends on the degree of pressure reduction. The results of the most important prospective studies on antihypertensive therapy indicate that reduction of systolic blood pressure by 10–12 mm Hg and diastolic pressure by 5–6 mm Hg allows the number of strokes to be reduced by 38% [15]. In addition, obtaining a diastolic pressure lower than or equal to 80 mm Hg as a result of treatment causes a 43% reduction in the incidence of stroke in relation to people with a pressure less than or equal to 90 mm Hg [16]. Perhaps this is the answer to the question of the optimal value to which blood pressure should be lowered to reduce the risk of stroke.

Diabetes is combined with both large and small vessel disease, and the relative risk of stroke in patients with diabetes is estimated from 1.8 to 6.0, with that of the male and female population being 4.1% and 5.8%, respectively, on average [17]. The risk depends on the type and severity of the disease [18]. The risk of stroke in diabetic patients increases when the patient with diabetes also has other risk factors for stroke [19].

Smoking is a major cause of disability and deaths, being responsible for 6.3% of all illnesses [20]. Based on many multicenter studies, smoking has been confirmed as an important and independent risk factor for IS. Smokers are 2 to 4 times more likely to have ischemic strokes than non-smokers, regardless of the presence of other risk factors [21, 22].

Dyslipidemia is the main risk factor for coronary heart disease; its role in the pathogenesis of ischemic stroke, initially unclear, is now more and more appreciated. Dyslipidemia and cigarette smoking are responsible for insulin resistance and are modifiable risk factors for vasculopathy. Insulin resistance causes inhibition of lipogenesis, lipolysis intensification, and thus an increased concentration of free fatty acids and triglycerides in the blood [23]. The risk of the first IS is reduced by 21% for each LDL-C reduction by 1 mmol/l. This effect is similar in men and women [24, 25]. Beneficial effects persist over long-term observation. In the United Kingdom Prospective Diabetes Study in people with newly diagnosed type 2 diabetes, an increase in HDL by 3.86 mg/dl reduced the risk of stroke by 15% [26].

This study had several of limitations inherent to its retrospective cohort methodology. This was a single-center study, with a limited number of TINR patients. We selected only the most common stroke risk factors. Further prospective studies with a larger sample size are needed.

In conclusion, as evidenced by our results, in patients with NVAF and co-existing thromboembolic risk factors, warfarin treatment and INR index in the 2.0–3.0 range are insufficient to protect this group of patients against an IS. Increasing INR to more than 3, recommended by some authors, or replacing old generation anticoagulants with new generation oral anticoagulants also will not protect the patients with NVAF and thromboembolic concomitant factors against IS [27–30]. This is due to the fact that, apart from NVAF, numerous other risk factors require the use of an antiaggregate agent. The combination of an anticoagulant with an antiaggregant, due to the significant risk of intracerebral hemorrhage, has so far not been justified in the secondary prevention of IS. This seems to increase the role of statins in addition to the recognized anticoagulant role in secondary prevention of stroke in patients with NVAF. In light of the above data, it seems increasingly important to modify the lifestyle of patients, including dietary treatment, ceasing smoking and, if possible, increasing physical activity.

## Conflict of interest

The authors declare no conflict of interest.

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