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## Original Research

# Evaluation of risk factors and drug adherence in the occurrence of stroke in patients with atrial fibrillation

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### Abstract

**Background:** Atrial fibrillation (AF) patients are at high risk of developing a stroke and anticoagulant medications are generally prescribed to prevent stroke in AF population.

**Objective:** This study aims to evaluate stroke risk factors among hospitalized patients with AF and to assess the level of adherence to medications in AF patients and their relation with stroke.

**Methods:** This is a case-control study conducted between June 1<sup>st</sup>, 2018 and December 31<sup>th</sup>, 2018 among AF patients admitted to seven tertiary Lebanese hospitals. Data were collected using a standardized questionnaire. Adherence to medications was assessed using the Lebanese Medication Adherence Scale-14. Odds ratios (OR) expressed the strength of association between the independent variables and the dependent variable and were estimated using unconditional logistic regression adjusted for confounding factors.  $P < 0.05$  determined statistical significance.

**Results:** In total, 174 cases of AF patients were included with 87 cases and 87 controls. The risk of stroke among AF significantly increased with the presence of a history of hypertension, aOR 16.04 (95%CI, 2.27-113.37;  $p=0.005$ ), history of coronary heart disease/myocardial infarction, and history of obesity. Anticoagulant medication significantly decreased the risk of stroke among AF patients, aOR 0.27 (95%CI, 0.07-0.98;  $P=0.047$ ). High adherence to medications was significantly associated with a reduced risk of stroke, aOR 0.04 (95%CI, 0.01-0.23;  $p<0.001$ ).

**Conclusions:** Having a history of hypertension is one of the strongest risk factors for stroke among AF patients in Lebanon. While anticoagulant medication use was associated with a reduced risk for stroke, high adherence to medications is critical for stroke prevention. Public health interventions are needed to tackle low-adherence to medication and prevent stroke among AF patients.

### Keywords

Atrial Fibrillation; Stroke; Inpatients; Risk Factors; Anticoagulants; Medication Adherence; Hypertension; Coronary Disease; Obesity; Odds Ratio; Logistic Models; Case-Control Studies; Lebanon

## INTRODUCTION

The World Health Organization defines stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin”.<sup>1</sup> The Middle East has limited information in regard to stroke, including Lebanon.<sup>2</sup> However, a recently published study in Lebanon identified atrial fibrillation history as one of stroke risk factors, OR 2.67 (95%CI, 1.16-6.11;  $p=0.02$ ).<sup>3</sup>

According to the Framingham study, Atrial Fibrillation (AF) is a significant risk factor for stroke, increasing the relative risk of ischemic stroke by 4 to 5 times.<sup>4</sup> Among people

older than 70 years of age with AF, it is estimated that the absolute stroke rate averages about 3.5% per year, however, this rate may increase significantly depending on age and other clinical features.<sup>5</sup> Advanced age, hypertension, diabetes, and previous stroke or transient ischemic attack (TIA) are four key risk factors that have been independently associated with stroke in AF patients as has been demonstrated in many studies.<sup>5</sup>

Anticoagulant medications should be used in most patients with AF to prevent stroke.<sup>6</sup> Many prospective randomized controlled trials documented the beneficial outcome of anticoagulant with warfarin for stroke prevention among AF patients.<sup>7</sup> Despite the significant effectiveness of anticoagulant therapy for stroke prevention, strict adherence to medication is vital for treatment success.<sup>8,9</sup> The World Health Organization defines medication adherence as “the extent to which a person’s behavior, taking medication, following a diet, and/or executing lifestyle changes, corresponds to agreed recommendations from a healthcare provider”.<sup>10</sup> Currently, it is estimated that only 1 out of 6 patients perfectly adhere to their medication, and data from ATRIA study (AnTicoagulation and Risk Factors In Atrial Fibrillation) suggests that 25% of newly prescribed patients of warfarin will discontinue in almost one year.<sup>11</sup> Serious and fatal bleeding is usually a major concern associated with anticoagulant with warfarin treatment, RR 1.56 (95%CI, 1.03-2.37).<sup>12</sup> This is also confirmed in a cross-sectional study conducted in Turkey to measure adherence to non-vitamin K antagonist oral

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anticoagulants where nonadherence had been related to stroke rates (5.6% vs 2.5%,  $p<0.001$ ), and minor and major bleeding rates, (21.2% vs 11.1%,  $p<0.001$ ) and (6.1% vs. 3.7%,  $p=0.004$ ), respectively.<sup>13</sup> Additionally, in 12 months follow-up of 2259 patients with AF, the multivariate analysis indicated that nonadherence to antithrombotic treatment was associated with an increased risk of stroke for primary prevention, OR 2.95 (95%CI, 1.26-6.90) and recurrent stroke for secondary prevention, OR 2.80 (95%CI, 1.25-6.27) as well as all cause death, OR 2.75 (95%CI, 1.33-5.69).<sup>14</sup>

In this study, we aimed to evaluate stroke risk factors among hospitalized patients with AF and to assess the level of adherence to medications in AF patients and their relation with stroke.

## METHODS

### Study design

This is a case-control study conducted between June 1<sup>st</sup>, 2018 and December 31<sup>th</sup>, 2018. Adult participants were selected from 7 tertiary hospitals in Lebanon (private and governmental hospitals). Cases were AF patients admitted to the included hospitals with a stroke diagnosis confirmed by brain computed tomography (CT) scan or magnetic resonance imaging (MRI). Controls were AF patients admitted to the participating hospitals during the same time period of cases with a diagnosis other than stroke. This study didn't require an institutional review board approval because it is only observational with no traceability of patients. However, a verbal consent was obtained from each patient prior to the participation in the study.

### Data collection

Data were collected prospectively by the main researcher of the study based on information present in the patient's hospital file or from patients. We used a standardized questionnaire written in English and translated into Arabic. The questionnaire was pilot tested in Arabic language on a small group of individuals in order to exclude any potential contradictions. It included five sections related to patient's identification and diagnosis, socio-economic and demographic factors, stroke risk factors, medications, and laboratory data. The main researcher of the study approached the patient or a relative - if the patient was incapable of answering - with the questionnaire and personally collected the answers. A relative must be a person living with the patient and knowing about the patient's medical history and medication in order to answer the questionnaire.

### Sample size calculation

The sample size calculation was performed using Epi Info Program, assuming a 5% alpha risk, a study power of 80%, and a case: control ratio of 1:1. As, no data was found in the literature regarding the percentage of exposure among controls (AF patients non-adhering to anticoagulant medications and free of stroke), therefore a 50% of controls exposed was considered. In addition, according to Mazurek *et al.*, the odds ratio of stroke risk for primary prevention in non-adhering patients is 2.95.<sup>14</sup> As a result,

the total sample size required was 122 AF patients with 61 cases and 61 controls.

### Assessment of the adherence to medications

The list of medications assessed in this study includes antihypertensive, lipid-lowering, anti-diabetes, anticoagulant, aspirin, clopidogrel, and anti-depressant medications. Adherence to medications was assessed using the fourteen-item LMAS-14 (Lebanese Medication Adherence Scale-14).<sup>15</sup> The LMAS-14 is a validated and practical tool used to assess adherence to medications among Lebanese hypertensive patients. However, this scale may also be used to measure patients' adherence to treatment in chronic diseases. The LMAS-14 contains 14 questions related to occupational, psychological, annoyance, and economical factors that may interfere in patient's adherence to treatment. Each question has 4 answers for the patient's to choose from, ranging from low adherence (code 0) to high adherence (code 3). Therefore, a patient's score may range from 0 (lowest adherence) to 42 (highest adherence). A cut-off point of 38 is used to class patients as adherent or non-adherent to medications.<sup>15</sup> For this study, we calculated each patient's score on LMAS-14 in order to assess adherence to treatment.

### Statistical analysis

Data were analyzed using SPSS version 24. Bivariate and multivariate analyses were conducted. Continuous variables were presented as means with standard deviation and categorical variables as percentages. Sample t-test analyzed the difference in baseline characteristics between stroke and stroke-free patients for quantitative variables and Chi-square test analyzed the difference for qualitative variables. Fisher's exact test was used when the expected cell size was less than 5. ANOVA was used instead of t-test to compare the means of more than two groups. Only variables with  $p<0.2$  in the bivariate analysis were included in the multivariate logistic regression. Odds ratio expressed the strength of association between the independent variables (stroke risk factors / adherence to medication) and the dependent variable (presence of stroke or not) with 95% confidence interval.  $P<0.05$  determined statistical significance.

## RESULTS

In total, 174 cases of AF patients were admitted to the 7 hospitals between June 1<sup>st</sup>, 2018 and December 31<sup>th</sup>, 2018 with 87 patients admitted for stroke diagnosis and 87 patients admitted for diagnosis unrelated to stroke. All AF patients admitted to the 7 participating tertiary hospitals (governmental and private), agreed to be included in the study. However, no statistically significant differences between hospitals was found (one-way ANOVA test  $p=0.416$ ). Among included stroke cases, 10.3% had TIA, 17.2% had hemorrhagic stroke, and 72.4% had ischemic stroke. Moreover, 78.2% had CT scan, 16.1% had MRI, and 5.7% had both imaging techniques. None of the control patients had a CT scan or MRI.

The mean age of stroke was 72 (SD 10) years. Stroke patients statistically differed from stroke-free patients in regard to age ( $>65$  years) and sex (female). The majority of stroke patients were unemployed, married, medically insured, and had a lower education level (Table 1).

Variables	Total (N=174)	Stroke Patients (N=87)	Stroke-free Patients (N=87)	p-value
Age in years, mean (SD)	71.63 (10.17)	72.43 (9.63)	70.84 (10.67)	0.280
Age in categories, (N%)				0.040*
< 65 years	47 (27.0)	17 (19.5)	30 (34.5)	
> 65 years	127 (73.0)	70 (80.5)	57 (65.5)	
Sex, N(%)				0.044*
Male	70 (40.2)	28 (32.2)	42 (48.3)	
Female	104 (59.8)	59 (67.8)	45 (51.7)	
Employment status, N(%) <sup>€</sup>				0.080
Unemployed	101 (64.7)	50 (72.5)	51 (58.6)	
Retired	41 (26.3)	12 (17.4)	29 (33.3)	
Employed	14 (9.0)	7 (10.1)	7 (8.0)	
Education N(%) <sup>€</sup>				0.468
Low education <sup>μ</sup>	86 (92.5)	52 (91.2)	34 (94.4)	
Intermediate	3 (3.2)	1 (1.8)	2 (5.6)	
Secondary	1 (1.1)	1 (1.8)	0 (0)	
Higher education	3 (3.2)	3 (5.3)	0 (0)	
Marital status, N(%) <sup>€</sup>				0.684
Single	1 (1.1)	1 (1.8)	0 (0)	
Married	53 (57)	31 (54.4)	22 (61.1)	
Widowed/Divorced	39 (42)	25 (43.9)	14 (38.9)	
Medical insurance, N(%) <sup>€</sup>				0.518
Insured	97 (61.0)	51 (58.6)	46 (63.9)	
Uninsured	62 (39.0)	36 (41.4)	26 (36.1)	

\*, statistically significant; <sup>€</sup>, Missing data for some patients: considered missing at random in the analysis; <sup>μ</sup>, elementary education or no education

Stroke patients statistically differed from stroke-free patients in respect to anticoagulant, aspirin, and clopidogrel medications. They also differed in regard to medical history including hypertension, diabetes, coronary heart disease/myocardial infarction, peripheral artery disease, previous TIA/stroke, and family history of stroke as well as physical activity, waterpipe smoking (Table 2).

Stroke patients also showed significantly higher values of blood pressure than stroke-free patients.

Among the 174 included AF patients, only 49 patients were under oral anticoagulant treatment with 17 (34.7%) patients being admitted for stroke diagnosis. Around 88 AF patients were taking aspirin alone where 51 (58%) patients

Variables N(%)	Total (N=174)	Stroke Patients (N=87)	Stroke-free Patients (N=87)	p-value
Medication History				
Antihypertensive	157 (90.2)	77 (88.5)	80 (92)	0.611
Lipid lowering medication	67 (38.5)	37 (42.5)	30 (34.5)	0.350
Anti-diabetes	55 (31.6)	29 (33.3)	26 (29.9)	0.745
Antidepressant	26 (14.9)	16 (18.4)	10 (11.5)	0.288
Anticoagulant	49 (28.2)	17 (19.5)	32 (36.8)	0.018*
Aspirin	88 (50.6)	51 (58.6)	37 (42.5)	0.048*
Clopidogrel	29 (16.7)	19 (21.8)	10 (11.5)	0.103
Medical History				
Hypertension	144 (82.8)	82 (94.3)	62 (71.3)	<0.001*
Diabetes Mellitus	64 (36.8)	37 (42.5)	27 (31.0)	0.157
Dyslipidemia	62 (35.6)	31 (35.6)	31 (35.6)	1.000
Coronary Heart Disease/Myocardial Infarction	67 (38.5)	51 (58.6)	16 (18.4)	<0.001*
Peripheral Artery Disease	21 (12.1)	14 (16.1)	7 (8)	0.161
Heart Failure	44 (25.3)	23 (26.4)	21 (24.1)	0.862
Deep Venous Thrombosis/Pulmonary Embolism	19 (10.9)	10 (11.5)	9 (10.3)	1.000
Chronic Kidney Disease	20 (11.5)	10 (11.5)	10 (11.5)	1.000
Obesity	78 (44.8)	45 (51.7)	33 (37.9)	0.093
Previous TIA/stroke	30 (17.2)	30 (34.5)	0(0)	<0.001*
Physically active <sup>μ</sup>	41 (23.7)	17 (19.3)	27 (30.6)	0.223
Cigarette smoking status				0.126
Non-smokers	107 (61.5)	49 (56.3)	58 (66.7)	
Current smokers	56 (32.2)	34 (39.1)	22 (25.3)	
Previous smokers	11 (6.3)	4 (4.6)	7 (8)	
Waterpipe smoking status				0.019*
Non-smokers	157 (90.2)	73 (83.9)	84 (96.6)	
Current smokers	11 (6.3)	9 (10.3)	2 (2.3)	
Previous smokers	6 (3.4)	5 (5.7)	1 (1.1)	

\*, statistically significant; <sup>μ</sup>, a patient was considered physically active based on the WHO recommendations: 150 minutes of moderate physical activity per week, or 75 minutes of vigorous physical activity per week, or a combination.<sup>16</sup>

Table 3. Factors associated with the risk of stroke among atrial fibrillation patients			
Variable	aOR	95%CI	p-value
History of Hypertension	16.04	2.27-113.37	0.005*
History of coronary heart disease/myocardial infarction	5.15	1.75-15.14	0.003*
History of Obesity	4.93	1.7-14.26	0.003*
Anticoagulant	0.27	0.07-0.98	0.047*
OR <sub>a</sub> , Adjusted Odds Ratio; CI, Confidence Intervals; *, statistically significant; -2 Log likelihood 109.815; Nagelkerke R Square 0.653			

developed a stroke. Both medications, oral anticoagulant and aspirin, were taken by 13 patients and 5 patients (38.5%) developed a stroke. However, 50 AF patients were not taking neither oral anticoagulant nor aspirin and 24 patients (48%) were admitted for stroke diagnosis (data not shown).

In the multivariate logistic regression model, age ( $\geq 65$  years), gender and employment were considered as confounding factors and controlled in the analysis. The risk of stroke among AF patients significantly increased with the presence of a history of hypertension, aOR 16.04 (95%CI, 2.27-113.37;  $p=0.005$ ), history of coronary heart disease/myocardial infarction, and history of obesity. Anticoagulant medication was significantly associated with a reduced risk of stroke among AF patients, aOR 0.27 (95%CI, 0.07-0.98;  $P=0.047$ ) (Table 3).

The cut-off point 38 was considered to classify patients on LMAS-14 as adherent or non-adherent to medications. Around 6 AF patients were excluded from this analysis since they were not taking any medications prior to their admission to the hospital (patients did not know of their AF conditions prior to admission to the hospitals). Among the 168 patients included in the analysis of adherence to medication, 82 patients were admitted to the hospital for a stroke diagnosis and 86 patients were not admitted for stroke diagnosis. About 56 stroke patients (68.3%) had a high adherence to medication compared to 83 stroke-free patients (96.5%) ( $p<0.001$ ).

In the multivariate model, adherence to medications was assessed after adjustment on all potential confounders including socioeconomic and demographic, vascular, behavioral, and stroke risk factors. High adherence to medications was significantly associated with a reduced risk of stroke among AF patients, aOR 0.04 (95%CI, 0.01-0.23;  $p<0.001$ ) (Table 4).

## DISCUSSION

This study confirms that a history of hypertension, coronary heart disease/myocardial infarction and obesity may increase the risk of stroke among AF population. Taking oral anticoagulant medication decreases the risk of stroke. Moreover, high adherence to medication is found to be

statistically and significantly associated with a reduced risk of stroke.

Atrial fibrillation is an independent risk factor for stroke. AF patients have double the risk of death from stroke compared to stroke patients with other stroke causes and surviving patients are often left with increased disability.<sup>17</sup> Many studies identify increasing age as an important factor to be associated with stroke among AF patients.<sup>18-20</sup> It is estimated that 84% of the AF population ages 65 years and above and that 32% are older than 80 years of age.<sup>18</sup> Our results are in line with those findings where 80.5% of our AF sample is above 65 years of age and around 26.4% is more than 80 years old. However, our evidence was inconclusive that increased age is an independent predictive of stroke, probably due to a low number of subjects included in the study.

A history of hypertension is a powerful and consistent risk factor for stroke among AF patients.<sup>18,19</sup> Our findings confirm the strong relationship between AF and hypertension with aOR 16.04 (95%CI, 2.27-113.37;  $p=0.005$ ) as well as a statistically significant association between coronary heart disease/myocardial and stroke among AF patients, which is in correlation with other published findings.<sup>21</sup> Therefore, this study agrees with a recently conducted research in Lebanon where hypertension and coronary heart disease/myocardial infarction were considered as predictive factors for stroke.<sup>22</sup>

According to Khoury and Jazra, AF patients in the Gulf and Middle East differ from the West mainly by being younger and having high prevalence of obesity, diabetes, and smoking.<sup>18</sup> However, it is expected that better management of stroke among this population would advance with the use of anticoagulant medicines.<sup>18</sup> In our sample, oral anticoagulant treatment showed a decrease in the risk of stroke, aOR 0.27 (95%CI, 0.07-0.98;  $p=0.047$ ). Anticoagulant treatment is recommended for AF patients to prevent stroke with the exclusion of patients at high risk of bleeding complications.<sup>23</sup> The percentages of stroke found in this study suggest a superiority of oral anticoagulant treatment compared to aspirin for stroke prevention with similar risk of hemorrhage. However, the purpose of this study was not to compare both treatment among AF patients, but it is essential to highlight the necessity of examining the underlying causes for reduced

Table 4. Adherence to medication and the risk of stroke among atrial fibrillation patients			
Variable	aOR	95% CI	p-value
High adherence to medication	0.04	0.01-0.23	<0.001*
History of hypertension	13.09	1.83-93.74	0.01*
History of coronary heart disease/myocardial infarction	3.58	1.24-10.34	0.018*
History of Obesity	4.26	1.43-12.72	0.009*
Current waterpipe smoking	4.95	1.23-19.89	0.024*
OR <sub>a</sub> , Adjusted Odds Ratio; CI, Confidence Intervals; *, statistically significant; -2 Log likelihood 102.054; Nagelkerke R Square 0.677			
Age ( $\geq 65$ years), gender, employment, history of hypertension, history of diabetes, history of coronary heart disease/myocardial infarction, history of peripheral artery disease, history of stroke/TIA, history of obesity, cigarette smoking, and waterpipe smoking were controlled in this multivariate analysis.			



prescription of anticoagulants among AF patients.

The effectiveness of aspirin for stroke prevention in AF patients remains unclear particularly for cardioembolic stroke especially as anticoagulant has shown a superiority in success.<sup>24</sup> Aspirin is usually used among young patients with low risk of stroke or with those presenting contradictions to warfarin.<sup>5</sup> Our data showed that aspirin use was not restricted to a younger age among AF patients; 37.5% and 48.9% of patients were 61-70 and 71-90 years old, respectively.

Adherence to antihypertensive medication is believed to better predict the risk of stroke.<sup>22</sup> Many studies have demonstrated that low adherence to antihypertensive treatment is associated with high risk of stroke and cardiovascular diseases.<sup>25</sup> Additionally, low adherence to this medication among hypertensive patients increases the risk of dying from a stroke by 4 times by the second year of prescribed treatment compared to high adherent patients.<sup>26</sup> In this study, high adherence to medications, in general, has proved to be associated with reducing the risk of stroke among AF patients, aOR 0.04 (95% CI, 0.01-0.23;  $p < 0.001$ ). The percentages of adherence ((68.3%) among stroke patients and (96.5%) among stroke-free patients) were higher than the percentage of adherence reported in our previous study among Lebanese outpatients with chronic diseases (42.6%).<sup>27</sup> This could be explained by the fact that adherence to medications used to treat some other chronic conditions such as oral antidiabetic medication was found to be low for Lebanese patients as reported in our previous study among Lebanese diabetic patients.<sup>28</sup>

Our findings also suggest that more stroke risk factors are found to be predictors of stroke along with high adherence to medications, including hypertension, coronary heart disease/myocardial infarction, obesity, and waterpipe smoking. For instance, among the 174 patients included in the study, 157 patients were under antihypertensive treatment with 144 patients being hypertensive. And although hypertensive patients were prescribed antihypertensive medication, only 45.6% had a controlled blood pressure while 27.9%, 16.2%, and 10.3% had a grade 1, grade 2, and grade 3 blood pressure, respectively, indicating an issue in adherence to antihypertensive medications among this population.<sup>29</sup> This is similar to what was found in Lebanon with Matar and colleagues study in regards to hypertensive patients and antihypertensive

treatment, however, it is important to emphasize on the low adherence to this medication which resulted in uncontrolled blood pressure and stroke.<sup>30</sup> More studies are called for in order to assess why patients do not adhere accurately to their prescribed medications.

This study has many strengths: (1) this study is original in assessing the relationship between adherence to medications and stroke among AF patients in Lebanon; (2) data were included from 7 different tertiary hospitals in Lebanon in order to be as representative as possible of the Lebanese population; (3) data were collected prospectively; (4) common potential bias of case-control studies were controlled; cases and controls were from the same hospitals and a standardized questionnaire and protocol were used for data collection and analysis.

This study has also many limitations: (1) the limited number of subjects included didn't allow to better explore the relationship of certain risk factors and stroke among AF patients, including cigarette and waterpipe smoking; (2) classification bias may have had an impact on the adherence to medication since this is a self-reported questionnaire and some patients may have provided socially desirable responses in regard to their adherence to medications.

## CONCLUSIONS

In conclusion, our findings suggest that having a history of hypertension is the strongest risk factor for stroke among AF patients in the Lebanese population along with other important factors. While anticoagulant medication use was associated with a reduced risk for stroke, high adherence to medications is critical for stroke prevention. Implementing public health interventions are needed in order to tackle low-adherence to medication in AF population and reduce the number of stroke.

## CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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