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# **PhD THESIS**

**CARDIO-NEUROLOGIC ASSOCIATION IN  
PATIENTS WITH PERMANENT ATRIAL  
FIBRILLATION**

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**KEYWORDS:** atrial fibrillation, neuropsychiatric complications,  
 cerebrovascular accident, dementia

## INTRODUCTION

Although the subject of atrial fibrillation is intensely discussed, it remains relevant due to the lack of screening protocols for patients prone to develop atrial fibrillation as a complication of pathological conditions, as well as due to the lack of effective curative methods able to stop the entire array of neuropsychiatric complications associated with the evolution of atrial fibrillation.

Current research has highlighted the involvement of risk factors such as age, male gender, diabetes, heart failure in the occurrence of atrial fibrillation (AF). Their involvement is being evaluated and extensive clinical trials are still needed to determine their degree of involvement in the genesis and self-maintenance of atrial fibrillation.

Multiple studies provide conflicting data on the impact of comorbidities and their treatment.

Metformin, thiazolidinediones and dapagliflozin appear to have a protective effect on the occurrence of atrial fibrillation in diabetic patients.

Anticoagulant treatment is currently the most effective tool in the prevention of embolic cerebrovascular accidents (strokes), with relatively low costs. Multiple studies

have demonstrated the effectiveness of anticoagulation using either vitamin K antagonists or direct anticoagulants in stroke prevention. However, anticoagulation is not fully effective, as there are not only cardioembolic events, but also hemorrhagic cerebral events (as a complication of anticoagulation). Hence the legitimate question: can we predict these events using other tools than the current ones (risk scores for bleeding or stroke)? We could then better identify patients at risk of developing degenerative changes in the brain, cognitive changes, or depression as a natural course of atrial fibrillation.

The European Atrial Fibrillation Management Guide recommends restoring sinus rhythm whenever possible, with the aim of increasing the patient's quality of life by reducing or eliminating symptoms related to the presence of atrial fibrillation.

Various therapeutic approaches must often be used to restore sinus rhythm, often in combination.

Heart rate control should only be used if sinus rhythm restoration cannot be performed.

Personalized therapy seems to be the key to the success of controlling this pathology. The use of the patient's clinical characteristics, the dynamic interpretation of biomarkers, the non-invasive elucidation of the substrate (echocardiography, cardiac CT, cardiac MRI) contribute to a more efficient correction of the pathophysiological process underlying the occurrence and maintenance of this arrhythmia.

## **GENERAL PART**

This part of the paper is structured in four chapters and makes a brief presentation of the data on atrial fibrillation and its neuropsychiatric complications.

The first chapter of the general part highlights aspects related to the epidemiology of atrial fibrillation and cardioembolic stroke, defines atrial fibrillation

and reviews its classification according to the European cardiac management guide of 2020 of the European Society of Cardiology and the role of risk factors in its occurrence.

The section on risk factors in this chapter includes both the factors already known in the occurrence of atrial fibrillation but also factors on which there is still discussion or where the evidence to link them to atrial fibrillation is not yet conclusive enough.

In the continuation of the first chapter, aspects related to the new approach to the patient with atrial fibrillation proposed by the atrial fibrillation management guide from 2020, as well as therapy concepts in atrial fibrillation, are mentioned.

The second chapter of the general part details the aspects related to the eight most common risk factors encountered in patients with atrial fibrillation, highlighting the current evidence that attests the direct link between their existence and the occurrence of atrial fibrillation.

The third chapter details aspects related to the correlations between atrial fibrillation and neuropsychiatric complications.

The existence of a link between the presence of neuropsychiatric disorders prior to atrial fibrillation and the onset of atrial fibrillation was analyzed in the fourth chapter of the general part.

## **SPECIAL PART**

Atrial fibrillation is a rhythm disorder that affects millions of people, and the number of newly diagnosed patients is constantly increasing, while also increasing the costs of health systems for the care of these patients.

Atrial fibrillation is responsible for a growing morbidity and mortality, due to the debilitating complications that occur throughout its natural history or are generated by its treatment.

Understanding the pathogenic mechanisms, recognizing and counteracting the risk factors of atrial fibrillation are essential requirements if we want to reduce the burden induced by it, and especially by its complications.

Slowing down the progression of disorders that may be a substrate in the occurrence of atrial fibrillation should be a goal of every physician caring for patients with medical conditions. Recognition of these pathologies, treatment and monitoring of their evolution can be the first obstacle in the occurrence of atrial fibrillation. Upon their worsening, the practitioner must consider the active search (screening) of atrial fibrillation in order to introduce anticoagulant therapy, as well as therapy designed to restore and maintain sinus rhythm.

Detection of paroxysmal episodes of asymptomatic atrial fibrillation by various devices (24-hour Holter EKG monitoring, smartphones and smartwatches, various other medical or non-medical devices) should be done as soon as possible to avoid the occurrence of embolic cerebral complications (including but not limited to ischemic stroke, dementia, depression), and the tools that we currently have available are anticoagulant therapy and therapy that restores and maintains sinus rhythm.

Our study has the following objectives:

- the primary objective of this study is to identify the elements whose existence predisposes to the occurrence of neuropsychiatric complications in the patient with atrial fibrillation.
- the secondary objectives of this study are represented by:
  - determination of the time period in the evolution of the various risk factors necessary for the occurrence of atrial fibrillation
  - determining the advantages of using some drugs to the detriment of others, in order to delay as long as possible the neuropsychiatric complications
  - understanding the requirements for screening for atrial fibrillation in pathologies that may be complications of atrial fibrillation but which have no apparent reason

To achieve these objectives we conducted a retrospective study within the Internal Medicine Clinic of the Municipal Clinical Emergency Hospital Timisoara, on all patients discharged between January 1, 2015 - December 31, 2016, enrolled consecutively (depending on the date of discharge) using as sole criterion for inclusion the mentioning of atrial fibrillation among discharge diagnoses. This resulted in a study group of 1111 subjects.

These patients were subsequently divided into 2 subgroups based on the diagnosis made at discharge. Thus, a group included all patients diagnosed with paroxysmal atrial fibrillation (group 1) and included 388 patients, of which 192 women representing 49% of all subjects from this subgroup. The second group included patients diagnosed with permanent atrial fibrillation, including 723 patients, of which 387 women representing 54% of all subjects from this group.

During the analyzed period, the proportion of readmissions is approximately one third of the total hospitalizations for atrial fibrillation. For our study, however, only the data related to the first presentation with atrial fibrillation in the analyzed period were analyzed.

We analyzed the following aspects of our study group:

- demographic data: sex, age, place of origin, in-hospital death
- anthropometric data (height, weight, body mass index)
- particular thoracic conformations: asthenic, emphysematous, barrel-shaped
- information related to the mode of hospitalization (through the emergency department, or as a scheduled hospitalization), the patient's health status on hospitalization;
- associated comorbidities and time of onset from the date of first diagnosis of AF: chronic obstructive pulmonary disease, asthma, heart failure, hypertension, chronic coronary syndrome (stable angina pectoris – classified according to the Canadian classification, unstable angina pectoris, myocardial infarction history were analyzed), valvulopathies, pulmonary hypertension (echocardiographical estimation), diabetes mellitus, hyperuricemia, dyslipidemia, chronic kidney disease, anemia;



- the presence or absence of neuropsychiatric complications, the moment of their diagnosis compared to the first diagnosis of atrial fibrillation, the impact of multiple hospitalizations on them (stroke, cognitive impairment, dementia, Parkinson's disease, epilepsy, anxiety-depressive disorder, depression were analyzed);
- haematological or biochemical blood constants (complete blood count, erythrocyte sedimentation rate, fibrinogen, C-reactive protein, uric acid, sideremia, glycemia, serum creatinine and glomerular filtration rate estimated by Chronic Kidney Disease Epidemiology Collaboration, serum sodium, serum potassium, total serum cholesterol, HDL cholesterol, LDL cholesterol, serum triglycerides);
- the following echocardiographic parameters: left and right atrium size, right ventricle size, telediastolic and telesystolic diameters of the left ventricle, left ventricular ejection fraction, left ventricular diastolic function, presence of valvular regurgitation or stenosis, maximum regurgitant velocity, systolic pressure in the pulmonary artery.

The statistical analysis of the data highlighted aspects demonstrated by other studies, but also differing aspects.

Age is significantly increased in patients with permanent fibrillation compared to patients with paroxysmal atrial fibrillation.

Regarding the place of origin of the patients, it was found that for the group with permanent atrial fibrillation there are no statistically significant differences. For the group with paroxysmal atrial fibrillation, the proportion of patients from urban areas is significantly increased, life in urban areas being a significant risk factor for paroxysmal atrial fibrillation.

For our group there are several elements whose presence has statistically significant value in favor of permanent atrial fibrillation (chronic kidney disease, myocardial infarction, dilated cardiomyopathy, hypercholesterolemia, peripheral arterial disease).

For the group of patients with permanent fibrillation included in the present study, myocardial infarction, hypercholesterolemia and advanced age are statistically significant predictive (risk) factors.

The neuropsychiatric disorders investigated in our study are represented by ischemic stroke, hemorrhagic stroke, dementia, epilepsy, Parkinson's disease, cortical atrophy, cerebral lacunar syndrome, vertebrobasilar insufficiency, vertigo, headache.

Patients with paroxysmal AF have an increased risk of neuropsychiatric changes, with a factor of 1,848 compared to patients with permanent atrial fibrillation. In other words, the group of patients with paroxysmal atrial fibrillation has an 84.8% higher chance of neuropsychiatric changes compared to the group of patients with permanent atrial fibrillation.

Male patients have an increased risk of neuropsychiatric changes, by a factor of 1,657 compared to female patients, therefore males have a 65.7% higher chance of neuropsychiatric changes compared to females.

The risk of neuropsychiatric changes is higher for elderly patients. For each unit increase in age, the chance of neuropsychiatric changes is increased by a factor of 1,041, which means that an increase by one unit in age is associated with a 4.1% higher chance of neuropsychiatric changes.

In the presence of atrial fibrillation (whether paroxysmal or permanent) after logistic regression processing using the Enter method of the data obtained from our group we can conclude that obesity, atheromatosis, peripheral arterial disease and old age are significant predictors of ischemic stroke.

Applying the same statistical analysis separately for the two groups we observe that the predictive factors for the occurrence of stroke in patients with atrial fibrillation differ in the paroxysmal group versus the permanent one. Thus, chronic kidney disease, obesity and old age are predictive factors in the case of paroxysmal atrial fibrillation, whereas in the case of permanent atrial fibrillation, peripheral arterial disease and atheromatosis are predictive factors of stroke.

When looking at the two groups as a whole (all patients included in the study group), overweightness and/or obesity, myocardial infarction, chronic coronary syndrome (ischemic heart disease), hypertriglyceridemia, hyper-LDL cholesterolemia,

mixed dyslipidemia, hypertension and atheromatosis are pathologies significantly associated with the presence of ischemic stroke.

For patients with paroxysmal atrial fibrillation, the incidence of ischemic stroke is higher in the presence of the factors listed above, with 2 observations: obesity and overweightness do not influence the occurrence of stroke, but hypercholesterolemia has an important role in ischemic stroke.

In patients with permanent atrial fibrillation, stroke is significantly accompanied by the presence of hypertriglyceridemia, hyper-LDL cholesterolemia, mixed dyslipidemia, atheromatosis and arteriopathy. Patients with permanent atrial fibrillation with normal serum triglyceride levels have a lower incidence of stroke as opposed to those with hypertriglyceridemia, who develop this complication more frequently. By analyzing the presence of LDL cholesterol in patients with permanent atrial fibrillation, we can say that its normal values are less often associated with ischemic stroke even if atrial fibrillation is present, in contrast to patients with hyper-LDL cholesterolemia, who develop ischemic stroke more frequently.

Dementia, another dreaded complication of atrial fibrillation, is also influenced by the presence of additional risk factors that overlap with the existence of atrial fibrillation. In patients with paroxysmal atrial fibrillation, chronic coronary syndrome and asthma are significant risk factors for dementia. Body mass index above the upper limit of normal (overweightness and obesity) seems to have a protective role in the occurrence of dementia in patients with permanent atrial fibrillation, whereas mixed dyslipidemia and atheromatosis are comorbidities associated with permanent atrial fibrillation that significantly increase the risk of dementia. Chronic coronary syndrome (ischemic heart disease) adds a significant risk of dementia in patients with paroxysmal atrial fibrillation compared to patients diagnosed with paroxysmal atrial fibrillation in the absence of ischemic heart disease. Asthma has been shown to be an additional risk factor for dementia in patients with paroxysmal atrial fibrillation.

In the group of patients with permanent atrial fibrillation, the presence of an increased body mass index (above 25 kg/m<sup>2</sup>) has a significant protective role for the occurrence of dementia.

For the analyzed group, statistically significant correlations were observed between the presence of stroke and epilepsy, cortical atrophy, cerebral lacunar syndrome, cognitive decline, Parkinson's disease, dementia (other than Parkinson's disease), vertigo, anxiety-depressive disorder, and insomnia, but statistical significance could not be established for bipolar disorder, vertebrobasilar insufficiency, and headache.

For ischemic strokes detected by computed tomography of the skull, the existence of a statistical significance was determined in the case of alteration of the ejection fraction.

For most echocardiographic parameters, no statistically significant changes were observed, with a few exceptions: cerebral lacunar syndrome in relation to the left atrium; vertigo in relation to EDD, ESD, EDV; anxiety disorder in relation to EDV, ESV; depression in relation to right ventricle.

Statistical processing of CHA<sub>2</sub>DS<sub>2</sub>-VASc Score values related to neuropsychiatric complications revealed the following data with statistical significance: for stroke detected on cranial CT examination, cortical atrophy, cerebral lacunar syndrome, cognitive decline and Parkinson's disease, the relationship with anxiety-depressive disorder and depressive syndrome. The following correlations could be found between the CHA<sub>2</sub>DS<sub>2</sub>-VASc Score and some echocardiographic parameters: IVS values vary in the same direction (significantly increased or decreased IVS for increased or decreased CHA<sub>2</sub>DS<sub>2</sub>-VASc Score), LVPW values vary in the same direction (high or low LVPW for increased or decreased CHA<sub>2</sub>DS<sub>2</sub>-VASc Score), ESD values vary in the opposite direction to CHA<sub>2</sub>DS<sub>2</sub>-VASc Score values, i.e. ESD is significantly increased or decreased for decreased or increased CHA<sub>2</sub>DS<sub>2</sub>-VASc Score – weak inverse correlation; the same inverse correlation was also observed for EDV; SPAP values also vary in the same direction as the CHA<sub>2</sub>DS<sub>2</sub>-VASc Score – weak direct correlation.

## FINAL CONCLUSIONS

The inseparable link between the heart and the brain must never be omitted and the interdisciplinary approach to cardio-cerebral pathology is the key to the quality of life of patients in both medical specialties (cardiology and neurology / psychiatry).

The cardiologist must know the neurological complications of heart disease and the neurologist must know the cardiac sources of neurological diseases.

In patients with atrial fibrillation, anticoagulant treatment associated with attempts to control the heart rhythm, and, if this is not feasible, the heart rate, can slow the patient's neurological impairment by delaying the onset of dementia as much as possible.

Optimal control of atrial fibrillation risk factors appears to be the fourth pillar of treatment of patients with atrial fibrillation. The other mainstays are anticoagulant treatment, rhythm control and, if this cannot be obtained, ventricular rate control.

Patients with atrial fibrillation who have experienced a stroke in their disease history (whether it is transient ischemic, hemorrhagic or ischemic) require careful monitoring, in order to be able to therapeutically correct the manifestations of cognitive impairment, but more importantly require rethinking treatment regimens to effectively control other risk factors.

Cardiological evaluation is required in patients with neurological pathologies whose substrate has not yet been elucidated. Performing cardiac ultrasound to detect possible embolic sources is a must. Holter EKG monitoring for 24-72 hours or even longer or repeated can reveal their arrhythmic origin.

The diagnosis of cryptogenic stroke should be a last resort, the use of which should be made after intense attempts to document the arrhythmia in case of stroke, especially in the presence of highly trivialized manifestations such as vertigo, headache or even depression.

Periodic monitoring by 24-hour Holter EKG in patients with heart failure is required to document episodes of paroxysmal AF and initiation of anticoagulant therapy to prevent ischemic stroke. Even in the absence of AF detection at 24-hour Holter EKG monitoring, patients with low ejection fraction heart failure may benefit from reduced incidence of cardioembolic stroke under anticoagulant therapy.

Neurological evaluation along with high-sensitivity brain imaging should become routine in patients with embolism-generating cardiac pathology (even if it is not atrial fibrillation) in order to achieve optimal secondary or tertiary prevention with anticoagulant medication.

The use of anticoagulant medication should be part of the routine of the clinician regardless of their specialty, and the fear of hemorrhagic side effects of this medication should not be exaggerated.

The limitations of this study are given by:

- retrospective character, as the analyzed data were obtained during hospitalization, without a standardized procedure for evaluation and treatment of patients with atrial fibrillation
- lack of high-sensitivity craniocerebral imaging investigations routinely performed in patients with atrial fibrillation may lead to the omission of asymptomatic strokes
- emergency brain CT is the most used craniocerebral imaging method, but its sensitivity is limited in detecting cerebral microhemorrhages, or cerebral leukoaraiosis.