

Cognitive Decline and Subclinical Atherosclerosis in Patients with Atrial Fibrillation and Vascular Risk Factors

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Recent evidence shows that many vascular risk factors (VRFs) contribute to the cognitive decline. The aim of the study was to evaluate the cognitive decline, depression and the occurrence of subclinical atherosclerosis and the association between cognitive decline and subclinical atherosclerosis in patients with atrial fibrillation (AF) and VRFs versus patients without AF but with VRFs. After statistical analysis, we concluded that cognitive decline is more common in patients with AF and VRFs than in those without AF, but with VRFs, and we consider it is mandatory to identify and prevent cognitive changes. Our findings suggest a direct association between cognitive decline and AF, age, risk factors, cognitive parameters, hemodynamic changes (LVEF) and subclinical atherosclerosis (IMT).

Keywords: cognitive decline, atrial fibrillation, vascular risk factors, subclinical atherosclerosis

AF is one of the most common cardiac arrhythmias with over 6 million people in Europe being diagnosed with this type of arrhythmia. It is estimated that 2.5% of the world's population has AF and its prevalence increases substantially with age, especially after the 50 years, and men have a 1.5 times higher risk than women to develop AF [1].

Patients affected by AF may have a poor quality of life, low functional status and impaired cardiac function. Statistics show that over the next 50 years its prevalence will be at least 2.5 times higher [1]. In patients diagnosed with AF, there is a greater risk to develop stroke or heart failure, and to die more rapidly compared to patients without AF [2].

AF can be seen in patients with the following pathologies: valvulopathy, cardiomyopathies, hypertension, heart failure, congenital heart defects, coronary heart disease, obesity, diabetes mellitus, thyroid dysfunction, chronic obstructive pulmonary disease, sleep apnea or chronic kidney disease. It is necessary to establish the correct and genuine diagnosis of AF and the main goal in the management of fibrillation is to prevent its complications [1]. AF is recognized as an independent risk factor for cerebrovascular disease, which may manifest itself as impairment of cognitive function and dementia [3].

It is known that AF will be more and more common, due to the ageing of the population. The increase of elderly patients with AF leads to the occurrence and evolution of cognitive disorders in them. Patients with mild cognitive impairment have a lower quality of life compared to patients with normal cognitive function, and these patients have an increased risk of morbidity. Patients diagnosed with dementia have a higher mortality risk than non-dementia patients. The diagnosis of cognitive impairment is based on clinical evaluation and memory test scores, which are closely correlated with the daily functional status of the patient.

More than 20% of people > 70 years of age have mild cognitive impairment (MCI). Information from the literature shows that there is a close relationship between AF and stroke in terms of occurrence and progression of cognitive impairment. [2] It is further attempted to establish a close relationship between AF, cognitive decline and dementia, independent of the presence of stroke, by analyzing subclinical atherosclerosis, cardiac performance and neuropsychological tests.

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Experimental part

The purpose of our study was to identify the premature cognitive decline using neuropsychological tests and onset of myocardial dysfunction using echocardiographic parameters of left ventricle function (LVEF) and also to detect the earliest signs of subclinical atherosclerosis using arterial parameter (IMT), in patients with AF and VRFs compared with patients without AF and VRFs.

We enrolled a total of 90 patients: 45 patients diagnosed with AF (paroxysmal, persistent or permanent) and VRFs vs. 45 patients without AF but with VRFs, all of them were admitted to internal medicine or neurology clinics. Inclusion criteria were: patients with AF and VRFs with no previous history of cognitive decline or dementia, treated with OACs or NOACs therapy. All standards regarding ethics and good clinical practice were followed throughout our study. For all patients, we performed biochemical analyses, clinical and echocardiographic evaluation, neuropsychological assessment including MMSE, MoCA, ADL, IADL and GDS. The clinical evaluation consisted of: medical history, clinical examination – and the following parameters were registered: heart rate [HR], systolic blood pressure (SBP) and diastolic blood pressure (DBP). The paraclinical assessment consisted of: blood tests, resting electrocardiogram (EKG), transthoracic echocardiography - including left ventricular parameters function and Doppler of the carotid artery and arterial parameters of subclinical atherosclerosis (IMT). AF was determined through cardiac physical examination and electrocardiography at rest, independently of its status: paroxysmal, persistent, or permanent. Cranial computed tomography was performed in selected cases and it was not mandatory cognitive decline diagnosis.

Transthoracic echocardiography was performed using a General Electric Vivid E9 ultrasound system with a 5 MHz transducer, using two-dimensional (2D) methods and transverse sections. Images were obtained in the following views: parasternal long – axis, short-axis of LV and apex, apical long-axis of the 4, 3 and/or 2 chambers. LV performance was assessed by measuring left ventricle ejection fraction (LVEF) using planimetry and calculated according to the formula: $LVEF \% = (LVEDD - LVESD) / LVEDD \times 100$. LV diastolic function was assessed by measuring transmitral flow, Doppler inflow signal in parallel alignment with mitral blood flow, in order to quantify the maximum velocity of early filling wave (E- wave). All echocardiographic examinations were performed by the same examiner and on the same machine.

Parameters of subclinical atherosclerosis

IMT evaluation was performed using a General Electric Vivid E9 ultrasound system with a linear array transducer of 9 MHz. Measurements were obtained in the distal common carotid artery (CCA), 1 cm from the flow divider, at the far wall level; 10 measurements were performed for each patient and mean values were registered.

Neuropsychological tests

Mini-Mental State Examination (MMSE)

MMSE is a wide indicator used in assessing cognitive function and screening for quantification of cognitive impairment. This parameter includes the study of several types of cognitive functions such as (attention, orientation, calculation, recall, language manipulation, including constructional praxis). The MMSE score is between 0-30 points and when it is below 24 points, it represents a predictor for the onset of cognitive impairment and dementia. The MMSE score can be different depending on the age and educational level of the patient [3, 4]. This score is often used to identify and analyze the presence of cognitive impairment, and to study the evolution of the cognitive disorders for each individual patient [3, 5].

Montreal Cognitive Assessment (MoCA)

MoCA is a widely used screening assessment for detecting cognitive impairment. The MoCA test is a 30-point test administered in approximately 10 min. The MoCA assesses several cognitive domains: Visuospatial abilities (3 points), the short-term memory recall task (5 points), a three-dimensional cube copy (1 point), a phonemic fluency task (1 point), executive functions (1 point) and a two-item verbal abstraction task (2 points). Concentration, attention, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), digits forward and backward (1 point each) and a serial subtraction task (3 points). Language is assessed using a three-item confrontation naming task with low-familiarity animals (3 points), the aforementioned fluency task and repetition of two syntactically complex sentences (2 points). Orientation to time and place is evaluated by asking the subject for the date and the city in which the test is occurring (6 points) [6]. MoCA is a very effective score in early identification of MCI and early signs of Alzheimer's disease compared to MMSE score. MoCA scores range between 0 and 30. A MoCA score of 26 or over is considered to be normal [6].

Activities of daily living [ADL] ADL is used in the field of healthcare on a very large scale and refers to daily care activities. This indicator is commonly used by healthcare professionals to assess the capacity or person's inability to

measure their functional status, especially in the elderly, with disabilities or with coronary diseases [7]. The ADL scale takes about 10 min for administration [8]. As far as these functional abilities are concerned at the beginning of their life, they are well managed by the patient, but with the occurrence of cognitive disorders, their performance begins to deteriorate. We used in our study the variation of ADL with 5 basic categories: personal hygiene, dressing, eating, maintaining continence and transferring/mobility. ADL scores are between 0 [reduced functionality] and 10 [high functionality] [7, 8].

Instrumental Activities of Daily Living (IADL)

Lawton's IADL scale was developed to evaluate more complex activities, such as daily practical activities, which are necessary for normal business functioning [e.g. cooking, financial management or shopping]. These activities are more complex and are lost to patients with cognitive impairment before normal daily activities measured through ADL scale. Using this IADL scale, we identify early cognitive decline in older people with those requiring short-term or long-term care [9]. This Lawton IADL scale requires 10 to 15 min for evaluation. It can be applied in the form of an interview with the patient, or in the form of a written questionnaire that the patient fills in and contains 8 items with a cumulative score from 0 [low functionality] to 8 [high functionality] [9].

Geriatric Depression Scale (GDS)

Although there are several methods used to assess depression, Yesavage created GDS that is more useful for the elderly population. This scale contains 30 questions and is utilized to identify depression in elderly. Patients answer these questions by yes or no. [10] For an easier evaluation, a shorter GDS version containing only 15 questions was developed [11]. This shorter version is easier to use and very often applied by medical staff in clinical trials. The shorter version of the GDS is also easily used in patients with cognitive impairment, where a greater number of questions might be difficult to apply. [12] We used this short version for this study. The 15-question GDS scale (GDS-15) has a specificity of 89% and a sensitivity of 92% for diagnostic criteria of depression [11, 12].

Statistical analysis was performed using SPSS program version 20.0. Results are expressed as percentages, mean value \pm standard deviation. Assessment of LV function, vascular parameters, memory tests and the activity of daily living, depression tests, blood tests, HR and blood pressure in both groups of patients were done using impaired T-test. CHA₂DS₂-Vasc score and use of OACs or NOACs in AF patients were calculated using paired T-test. The values for $p < 0.001$ and $p < 0.05$ were considered statistically significant.

Results and discussions

All 90 patients enrolled in our study had a mean age of 69.98 ± 9.89 [44 - 89 years]. Among them, 54 (60%) were females with a mean age between 71.26 ± 9.48 years and 36 (40%) were men with mean age 68.06 ± 10.30 years. 30 (33.3%) patients were younger than 65 years old and 60 were older than 65 years old (66, 7%).

45 patients with AF and VRFs had a mean age of 72.84 ± 9.69 [49 – 89 years]. Out of the total number, 41 patients (91.1%) had hypertension, 12 (26.7%) had diabetes mellitus, 24 (53.3%) were with dyslipidemia and 9 (20%) were smokers. (Table 1)

Table 1
PATIENT DEMOGRAPHIC DATA, VASCULAR RISK FACTORS (VRFs)

	All 90 patients	45 patients with AF and VRFs	45 patients without AF and with VRFs
	No. of patients/ mean \pm SD/[%]	No. of patients/ mean \pm SD/[%]	No. of patients/ mean \pm SD/[%]
Age	90/ 69.98 \pm 9.89	45/ 72.84 \pm 9.69/ 50	45/ 67.11 \pm 9.33/ 50
Sex/Male/age	36/ 68.06 \pm 10.30/ 40	17/ 71.41 \pm 9.76/ 37.8	19/ 65.05 \pm 10.08/ 42.2
Sex/Female/age	54/71.26 \pm 9.48/ 60	28/ 73.71 \pm 9.72/ 62.2	26/ 68.62 \pm 8.64/ 57.8
Vascular risk factors			
Hypertension	85/ 94.4	41/ 91.1	44/ 97.8
Diabetes mellitus	19/ 21.1	12/ 26.7	7/ 15.6
Dyslipidemia	50/ 55.6	24/ 53.3	26/ 57.8
Smoking	18/ 20	9/ 20	9/ 20
Peripheral arterial disease	5/ 5.6	1/ 2.2	4/ 8.9
Obesity	10/ 11.1	5/ 11.1	5/ 11.1
Coronary disease	36/ 40	20/ 44.4	16/ 35.6
Heart failure	38/ 42.2	25/ 55.6	13/ 28.9

LVEF<50% / LVEF>50% LVEDV>100/LVEDV <100	11/ 12.2 / 79/ 87.8 9/ 10 /81/ 90	10/ 22.2 / 35/ 77.8 6/13.3 / 39/ 86.7	1 / 2.2 / 44/ 97.8 3/ 6.7 / 42/ 93.3
CKD	26/43.18+/-17.36/ 28.9	18/ 40	8/ 17.8
Lacunar stroke	26/ 28.9	13/ 28.9	13/28.9
Minor stroke	11/ 12.2	9/ 20	2/4.4

Abbreviations: LVEF - Left ventricle ejection fraction, CKD –chronic kidney disease, LVEDV - Left ventricle end-diastolic volume

In this study, we noticed a statistically significant increase of parameters in the lipid profile (total cholesterol, LDL-cholesterol and triglycerides) for patients with AF and VRFs compared to patients without AF but with VRFs. ($p<0.05$) Hb and Ht statistically significant decreased in patients with AF and VRFs compared to patients without AF and with VRFs ($p<0.05$). Creatinine increased significantly from 0.92 ± 0.21 mg/dl in patients without AF + VRFs to 1.06 ± 0.26 mg/dl in patients with AF and VRFs ($p < 0.05$). INR and PT (%) significantly diminished in patients with AF and VRFs compared to patients without AF + VRFs ($p<0.05$).

The modifications noticed in the other biological parameters did not reach statistical significance in patients with AF and VRFs compared to patients without AF and VRFs (Table 2).

Table 2
BIOLOGIC PARAMETERS IN ALL PATIENTS AND IN PATIENTS WITH/WITHOUT AF + VRFs

	All patients	Patients with AF and VRFs	Patients without AF and with VRFs	p
	Mean +/- SD	Mean +/- SD	Mean +/- SD	
Total Cholesterol (mg/dl)	179.97 +/- 59.91	197.22 +/- 64.90	162.73 +/- 49.40	0.006
LDL Cholesterol (mg/dl)	126.90 +/- 51.90	140.00 +/- 57.90	113.80 +/- 41.77	0.016
HDL Cholesterol (mg/dl)	48.55 +/- 20.68	46.51 +/- 13.46	50.60 +/- 25.98	0.351
TG (mg/dl)	128.11 +/- 55.14	139.91 +/- 62.63	116.46 +/- 44.11	0.043
Hemoglobin (g/dl)	13.65 +/- 1.90	12.98 +/- 1.92	14.32 +/- 1.65	0.001
Hematocrit (%)	40.86 +/- 5.19	39.26 +/- 5.54	42.46 +/- 4.32	0.003
ESR (mm/h)	7.50 +/- 2.01	7.40 +/- 2.22	7.60 +/- 1.78	0.634
Thrombocytes ^x $10^3/\mu\text{L}$	228.38 +/- 60.36	226.71 +/- 64.75	230.06 +/- 56.32	0.794
Glycemia (mg/dl)	113.94 +/- 37.46	114.77 +/- 47.11	113.11 +/- 24.85	0.834
Creatinine (mg/dl)	0.99 +/- 0.25	1.06 +/- 0.26	0.92 +/- 0.21	0.009
Urea (mg/dl)	43.07 +/- 19.56	46.12 +/- 23.77	40.02 +/- 13.77	0.141
ALT (U/L)	28.32 +/- 20.19	30.22 +/- 26.86	26.42 +/- 9.78	0.376
AST (U/L)	25.40 +/- 16.93	28.75 +/- 22.75	22.04 +/- 6.25	0.062
CKMB (U/L)	16.95 +/- 9.02	19.06 +/- 11.31	14.83 +/- 5.23	0.026
Na (mmol/l)	140.68 +/- 2.71	140.77 +/- 2.96	140.60 +/- 2.48	0.768
K (mmol/l)	4.11 +/- 0.45	4.03 +/- 0.52	4.18 +/- 0.36	0.131
Uric acid (mg/dl)	6.15 +/- 1.61	6.23 +/- 1.79	6.08 +/- 1.42	0.667
INR	1.87 +/- 0.82	1.67 +/- 0.91	2.06 +/- 0.68	0.025
APTT(s)	27.86 +/- 7.13	29.15 +/- 8.78	26.57 +/- 4.71	0.087
PT (s)	23.30 +/- 11.11	21.09 +/- 11.43	25.51 +/- 10.44	0.059
PT (%)	60.58 +/- 31.65	69.63 +/- 31.34	51.52 +/- 29.61	0.006

Abbreviations: LDL - Low-density lipoprotein; HDL - High-density lipoprotein; TG - Triglycerides; ESR – erythrocytes sedimentation rate; AST - Aspartate aminotransferase; ALT- Alanine aminotransferase; CKMB - Creatine kinase MB; Na – Sodium; K - Potassium; INR - International normalized ratio; APTT – Activated partial thromboplastin time; PT - Prothrombin time.

Using 2D echocardiography in both groups of patients we observed statistically significant modifications of the following parameters: LA (mm) increased from 38.9 ± 4.8 in patients without AF to 45.2 ± 6.5 in patients with AF ($p < 0.001$). LVEF (%) significantly decreased from 59.08 ± 5.54 in patients without AF to 55.91 ± 8.55 in patients with AF ($p < 0.05$). We observed significant changes in other echocardiographic parameters: LVEDD and PASP increased statistically significant in patients with AF versus patients without AF ($p < 0.05$). From the entire lot of patients, 11 patients (12.2%) patients had a LVEF $< 50\%$. Out of the group of patients with AF + VRFs, 10 patients (22%) had an LVEF $< 50\%$.

We noticed that changes of LV diastolic dysfunction parameters (analyzed through transmitral flow – E-wave) did not reach statistical significance range in patients with AF + VRFs versus patients without AF and VRFs (Table 3).

Table 3
ECHOCARDIOGRAPHIC PARAMETERS IN BOTH GROUPS OF PATIENTS

	All patients	45 patients with AF and with VRFs	45 patients without AF and with VRFs	P
	Mean +/- SD	Mean +/- SD	Mean +/- SD	
LA (mm)	42.1 +/- 6.5	45.2 +/- 6.5	38.9 +/- 4.8	<0.001
IVS (mm)	11.7 +/- 2.0	12.0 +/- 1.8	11.5 +/- 2.2	0.289
LVPW (mm)	11.8 +/- 2.3	11.3 +/- 1.7	12.4 +/- 2.7	0.025
LVEDD (mm)	46.9 +/- 5.4	49.2 +/- 5.6	44.6 +/- 4.0	<0.001
LVEDS (mm)	23.7 +/- 6.5	22.6 +/- 7.3	24.9 +/- 5.5	0.096
LVEF (%)	57.50 +/- 7.39	55.91 +/- 8.65	59.08 +/- 5.54	0.041
LVESV (ml)	35.58 +/- 14.53	37.66 +/- 16.73	33.51 +/- 11.76	0.176
LVEDV (ml)	77.46 +/- 21.36	79.71 +/- 23.80	75.22 +/- 18.61	0.322
PSAP(mmHg)	40.04 +/- 11.41	43.66 +/- 11.53	36.42 +/- 10.18	0.002
E (m/s)	0.72 +/- 0.20	0.75 +/- 0.22	0.69 +/- 0.17	0.147

Abbreviations: LA – left atrial, IVS - interventricular septum, LVPW - Left ventricular posterior wall, LVEDD - left ventricular end-diastolic diameter, LVESD - left ventricular end-systolic diameter, LVEF - left ventricular ejection fraction, LVESV - left ventricular end-systolic volume, LVEDV - left ventricular end-diastolic volume, PSAP – pulmonary systolic arterial pressure, E - peak early diastolic transmitral flow velocity

Regarding hemodynamic parameters, statistically significant changes were observed in the HR (b/min), it increased from $71,38 \pm 10,07$ for patients without AF + VRFs to $78,29 \pm 17,72$ ($p < 0,05$) in patients with AF + VRFs. SBP and DBP variations reached statistically significant elevations in patients with AF and VRFs compared to patients without AF and VRFs ($p < 0.05$). IMT both left and right registered a significant augmentation in patients with AF and VRFs compared to patients without AF and VRFs ($p < 0, 05$) (Table 4).

Table 4
ASSESSMENT OF HEMODYNAMIC PARAMETERS AND IMT IN BOTH GROUPS OF PATIENTS

	All patients	Patients with AF and with VRFs	Patients without AF and with VRFs	p
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
HR (b/min)	74.83 \pm 14.75	78.29 \pm 17.72	71.38 \pm 10.07	0.026
SBP (mmHg)	132.11 \pm 19.71	137.67 \pm 23.68	126.56 \pm 12.74	0.007
DBP (mmHg)	78.61 \pm 12.91	82.00 \pm 13.24	75.22 \pm 11.77	0.012
IMT left (mm)	0.70 \pm 0.32	0.81 \pm 0.31	0.59 \pm 0.30	0.002
IMT right (mm)	0.68 \pm 0.34	0.81 \pm 0.35	0.56 \pm 0.29	<0.001

Abbreviations: SD – Standard Deviation, HR – heart rate, SBP – systolic blood pressure, DBP – diastolic blood pressure, IMT – intima-media thickness

MMSE decreased statistically significant from 28.13 ± 2.55 to 24.60 ± 4.55 ($p < 0.001$) and MoCA decreased statistically significant from 25.84 ± 4.45 to 22.53 ± 5.05 ($p < 0.001$) in patients with AF and VRFs compared to patients without AF and VRFs. ADL and IADL significant decrease and GDS-15 significant increase in patients with AF and VRFs compared to patients without AF and VRFs ($p < 0.05$) (Table).

Table 5
NEUROPSYCHOLOGICAL TESTS IN ALL GROUPS OF PATIENTS

	All patients	Patients with AF and with VRFs	Patients without AF and with VRFs	p
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
MMSE	26.37 \pm 4.09	24.60 \pm 4.57	28.13 \pm 2.55	<0.001
MoCA	24.19 \pm 5.01	22.53 \pm 5.05	25.84 \pm 4.45	0.001
ADL	9.43 \pm 1.01	9.11 \pm 1.22	9.76 \pm 0.60	0.002
IADL	6.73 \pm 1.65	6.09 \pm 1.89	7.38 \pm 1.05	<0.001
GDS-15	6.76 \pm 2.30	7.66 \pm 2.05	5.86 \pm 2.21	<0.001

Abbreviations: SD - Standard Deviation, MMSE - Mini-Mental State Examination Scale; MoCA - Montreal Cognitive Assessment Scale; ADL - Activities of Daily Living Score, IADL - Instrumental Activities of Daily Living Score; GDS-15 -15-question Geriatric depression scale[GDS].

Regarding the age above 65 years, from all the studied patients, 23 patients were with AF and VRFs and 27 patients were without AF and with VRFs. In this study patients MMSE significantly decreased from 27.96 \pm 4.64 in patients without AF to 23.79 \pm 3.03 in patients with AF and MoCA significantly decreased from 25.81 \pm 5.15 in patients without AF to 22.21 \pm 5.14 in patients with AF ($p < 0.05$). SBP, DBP, IMT left and right and GDS-15 were significantly increased and neuropsychological tests [ADL, IADL] were significantly decreased in patients with AF more than 65 years versus patient without AF more than 65 years. ($p < 0.05$)

Regarding the age of fewer than 65 years, 12 patients were with AF and VRFs and 18 patients without AF and with VRFs. In this 12 study patients with AF less than 65 years, the presence of AF did not influence statistically changes in neuropsychological tests, echocardiographic parameters, IMT or hemodynamic parameters.

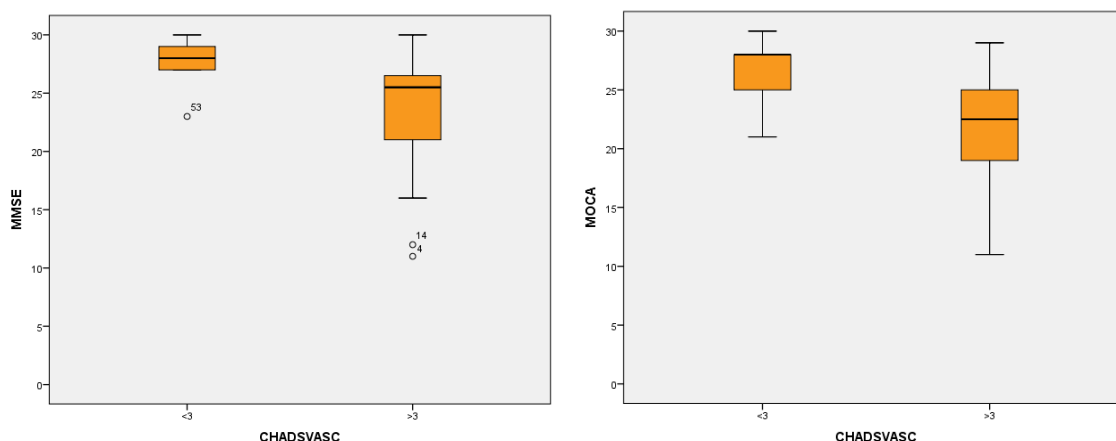


Fig. 1. MMSE and MoCA in patients with AF and VRFs with CHA₂DS₂-Vasc < or > 3

Out of 45 patients with AF and VRFs, 14 patients were with paroxysmal AF, 6 with persistent AF and 25 with permanent AF. CHA₂DS₂-Vasc was 3.66 \pm 1.43 and HAS-BLED 2.46 \pm 1.03 for all patients with AF. From all the patients with AF, 9 [20%] patients were with CHA₂DS₂-Vasc <3 (1 or 2) and 36 (80%) patients with CHA₂DS₂-Vasc >3.

MMSE significantly decreased from 27.78 \pm 2.16 in patients with AF and CHA₂DS₂-Vasc <3 compared with patients with CHA₂DS₂-Vasc >3 with MMSE 23.81 \pm 4.68 ($p < 0.05$). MoCA significant decrease from 26.56 \pm 2.96 to 21.53 \pm 4.98 in patients with AF and CHA₂DS₂-Vasc > 3 compared with patients with CHA₂DS₂-Vasc < 3 ($p < 0.05$). ADL significantly decreased and GDS significantly increased in patients with AF and CHA₂DS₂-Vasc >3 compared with patients with CHA₂DS₂-Vasc <3 ($p < 0.05$).

ADL significantly decreased from 9.79 \pm 0.42 in patients with paroxysmal AF to 8.81 \pm 1.35 in patients with persistent or permanent AF ($p < 0.05$). There were no differences between other neuropsychological parameters or vascular parameters in patients with different types of AF.

Out of the whole study group of AF patients regarding age, was noticed a significant decreased for both HR, from 87.25 \pm 21.23 to 75.03 \pm 15.36 ($p < 0.05$) and IMT right, from 0.089 \pm 0.029 to 0.060 \pm 0.041 ($p < 0.05$) in patients with AF age less than 65 versus patients with AF and age more than 65. Significant deterioration was noticed regarding neuropsychological tests regarding age: MMSE significant decrease from 26.83 \pm 3.66 to 23.79 \pm 4.63 ($p < 0.05$) and GDS-15 significant increase from 6.33 \pm 2.87 to 8.15 \pm 1.43 ($p < 0.05$).

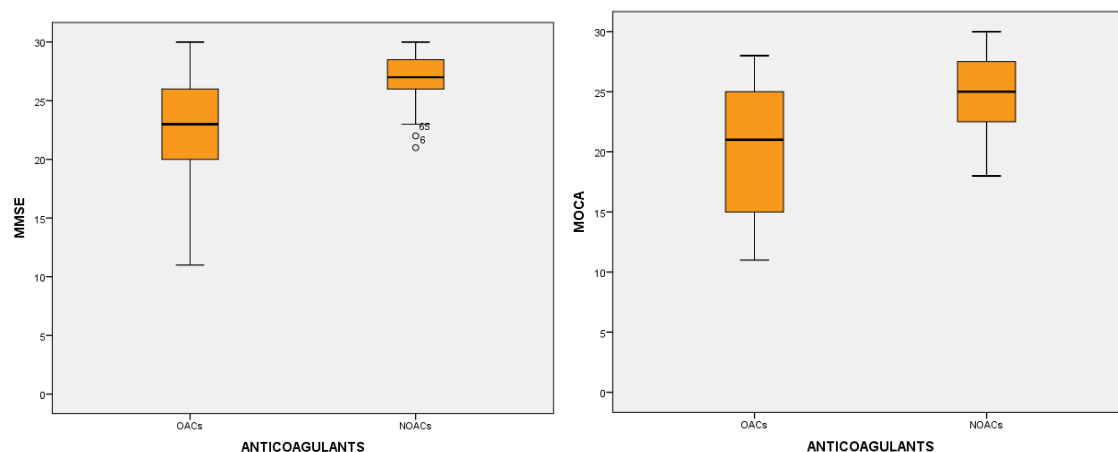


Fig. 2. MMSE and MoCA in patients with AF and VRFs treated with anticoagulants therapy [OACs or NOACs].

All patients with AF were with anticoagulants therapy. 21 patients were with oral anticoagulants using vitamin K antagonists (VKAs) - acenocoumarol therapy – (OACs) and 24 patients were with non-vitamin K antagonist oral anticoagulants therapy (NOACs). From that 24 patients on NOACs, 9 (10%) were on apixaban (direct factor Xa inhibitor) therapy, 11 (12.2%) on dabigatran (direct thrombin inhibitor) therapy and 4 (4.4%) on rivaroxaban (direct factor Xa inhibitor) therapy. MMSE significantly decrease from 26.67 ± 2.40 in patients with AF and NOACs to 22.24 ± 5.32 in patients with AF and OACs therapy. ($p < 0.05$) MoCA significantly decreased from 24.88 ± 3.12 in patients with AF and NOACs to 19.86 ± 5.55 in patients with AF and OACs therapy ($p < 0.05$). ADL significantly decreased in patients with OACs therapy than patients with NOACs therapy [$p < 0.05$]. IMT and left ventricular parameters diminished without statistically significance for patients with OACs versus NOACs therapy.

Regarding sex, in male patients MMSE significantly decreased from 28.16 ± 1.57 for patient without AF to 23.59 ± 4.90 compared to patients with AF ($p < 0.05$) and MoCA significantly decreased from 25.21 ± 4.15 in those without AF to 21.53 ± 5.30 vs. patients with AF ($p < 0.05$). ADL and IADL changes were noticed in male patients with AF and VRFs, with a significant decrease compared to those without AF; HR significantly increased in male patients with AF versus patients without AF ($p < 0.05$).

In female patients with AF and VRFs, we noticed that neuropsychological tests significantly changed: MMSE, MoCA, ADL, IADL significantly decreased and GDS-15 significantly increased compared to female patients without AF ($p < 0.05$). SBP and DBP significantly increased in female patients with AF versus female patients without AF ($p < 0.05$). IMT left and right significantly increased from 0.059 ± 0.030 (IMT left) respectively 0.054 ± 0.028 (IMT right) in female patients without AF to 0.084 ± 0.030 (IMT left) respectively 0.083 ± 0.034 [IMT right] in female patients with AF ($p < 0.05$).

Several findings have been revealed in this study. Regarding hemodynamic parameters HR (b/min), SBP (mm Hg) and DBP (mm Hg) variations reach statistical significant increase in patients with AF and VRFs, compared to patients without AF and with VRFs ($p < 0.05$). In the AFFRIM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) study, in post-hoc analysis of 3947 patients, there was an increase of 10 mm Hg in SBP and DBP from baseline. These data suggest that in patients with AF, the optimal BP target may be higher than the general population and the medication for treating AF can be associated with adverse events or all-cause mortality if BP is reduced to $< 110/60$ mmHg [13].

Hypertension is an extremely important risk factor and can be a predictor for AF development. The combination of hypertension and AF will be more common in the future due to the increasing population prevalence of both conditions [14]. From all our study patients, 85 (94, 4%) were with hypertension, and from all AF patients, 41 were hypertension, 14 patients were with paroxysmal AF and 31 with persistent or permanent AF. Hypertension was found to be predictive of arrhythmia progression from paroxysmal to persistent or permanent AF. [14] In European Heart Survey, during the 1-year follow-up, hypertension was more common in those who developed persistent or permanent AF versus paroxysmal AF patients (71% vs. 60%, HR 1.52, 95% confidence interval [CI] 1.05–2.20) [15]. One of the major components of AF management to improve patient outcomes is to optimize BP control. [14] In the RECORD-AF study (odds ratio 1.5, 95% CI 1.1–2.0), a prospective survey on AF management, this was further confirmed [16].

Patients with AF may experience reduced LVEF. [17] In our study, we observed statistically modifications of LVEF (%) with 3% significant decreased in patients with AF and VRFs and the values were between 47 - 63 % ($p < 0.05$). From the patients with AF and VRFs, 10 patients (22%) registered LVEF $< 50\%$. In a study involving 385 adults with newly diagnosed AF, patients who had AF and LVEF $< 55\%$ at the beginning were associated with longer-

term mortality of all causes. Those who subsequently recovered LVEF after medical therapy appears to have similar prognosis compared to those with LVEF > 55% initially [17].

The ARIC-NCS study (Atherosclerosis Risk in Communities Neurocognitive Study) analysed 6432 patients, of whom 611 (9.5%) had AF. AF was associated with an increased rate of MCI and dementia (CI 95%, 1.28, 1.04-1.562, respectively 2.5, 1.64-3.10). The prevalence of MCI / vascular dementia and MCI / dementia associated with Alzheimer's disease was higher in patients with AF than without AF (95% CI, 1.50, 0.99-2.25 and 1.29, 1.04 – 1.61). In multivariate analysis, lower body mass index, diabetes mellitus, older age and stroke were associated with the prevalence of dementia in patients with AF [18].

In patients without the manifest atherosclerotic disease, atherosclerosis is an independent risk factor for AF.[19] In our study IMT both left and right registered a significant increase at patients with AF and VRFs compared to patients without AF and VRFs ($p < 0.05$), with no significant changes between men or women. In another study, the risk of AF was associated with IMT (relative risk, 1.90; 95% CI, 1.20 -3.00) and severity of carotid plaques (relative risk, 1.49; 95% CI, 1.06-2.10). Risk estimates were stronger in women than in men. These results suggest that the correct treatment of asymptomatic atherosclerosis can prevent AF [19].

In a study included patients with amnesic MCI (an MCI) compared to controls, patients with an MCI were significantly older and had higher rates of AF, hypertension, depression and a larger IMT. [20] In another study on AF patients, young patients without risk factors and cardiac disease, AF was significantly associated with high carotid IMT and carotid-femoral pulse wave velocity [21]. IMT and / or atherosclerosis can be easily detected without risk and at low cost and can be incorporated into existing risk scores for AF to enhance their predictive precision. By preventing AF and atherosclerosis, cognitive disorders can also be prevented [22, 23].

In our study ADL and IADL significantly decreased and GDS significantly increased in patients with AF and VRFs compared to patients without AF and with VRFs ($p < 0.05$). The precision of the IADL scale is sensible even when patients experience MCI, while the accuracy of the ADL scale is higher when patients experience more severe cognitive impairment and dementia [24, 25]. Depression is associated with a substantial reduction in quality of life [26]. Depression can be seen more often with ageing. Both major and minor depressions were found in 13% of the elderly population. It has also been reported in 24% of older patients with medical pathology and 43% of patients requiring acute or chronic medical care at home [10]. The relationship between depression and MCI is complex. While a meta-analysis identifies depression as a risk factor for MCI [27], other studies evaluating depression and MCI, have found an association with prevalence but not incidence. These findings suggest that depression accompanies MCI but does not precede it [28]. Depression should not be considered as normal in the elderly, it should be recognized and treated as promptly as possible, if it is not treated in time, it can lead to social, physical or cognitive disorders [10].

In a meta-analysis, it has been shown that AF is associated with increased risk of MCI and dementia, whether or not the patients have a history of stroke [29]. In our study from the AF patients, 13 [28.9%] had lacunar infarcts and 9 [20%] minor stroke. In a study that tracked 707 patients after an ischemic stroke, AF was independently associated with lower MMSE scores, thus being associated with a higher risk of developing MCI (odds ratio 1.6, 95% CI 1.03-2.47, $P = 0.03$) [30] AF has an increased risk of TIA or stroke, as well as the occurrence of cognitive decline and dementia, whether or not the patient has cerebral vascular pathology [31]. In order to follow the association between the occurrence of cognitive decline and AF, several mechanisms have been identified: micro-lesions, pro-inflammatory conditions, silent cerebral ischemia [SCI] and altered cerebral blood flow dynamics [32].

As for patients with non-stroke AF, in a study involving 5150 participants, of whom 552 (10.7%) had AF on a 7-year follow-up period, cognitive impairment occurred more quickly in AF patients than in non-AF patients. Patients with AF have a higher risk of developing cognitive impairment at younger ages than patients with no history of AF. In patients over 75 years of age who developed AF compared to those without AF, there was a decrease of about 3 points on the cognitive decline scale as the age increased from 5 to 5 years [33].

In more than half of the 27 articles evaluated in a metathesis, in patients after a stroke, it was highlighted that age, educational level, diabetes, hypertension, type, size, and stroke are significant risk factors for MCI. Of the emotional disturbances presented, the symptoms of depression seem to have an important effect on cognitive disorders. These results are beneficial in addressing the strategy of preventing and managing cognitive impairment in patients after a stroke [34].

From studies comparing patients with AF versus patients without AF, contain the most important evidence of the relationship between AF and cognitive decline [35]. In our study MMSE and MoCA decreased statistically significant in patients with AF and VRFs compared to patients without AF and VRFs. ($p < 0.001$) In other studies conducted in Europe and the US, AF prevalence was closely associated with an MCI and global impairment of cognitive function. [36,37] In a study in Germany on detailed cognitive assessments, a group of patients without stroke, of whom 122 patients with AF versus 564 without AF, revealed that patients with AF showed significantly lower performance in terms of memory, learning, and executive functions [38].

The Rotterdam Study, which included 6548 participants over the age of 55 years, was among the first studies to highlight an association between AF and cognitive impairment, with the prevalence of dementia being more than double among AF patients compared to non-AF patients. The association was greater in patients less than 65 years of age and more common in females. [39] In the study of the Cardiovascular Health Study, which followed patients for a period of 7 years, the occurrence of AF was associated with the faster occurrence of cognitive impairment by lowering the MMSE score [40].

In our study, ADL significantly decreased in patients with paroxysmal AF, compared with patients with persistent or permanent AF ($p < 0.05$). In our patients with AF, patients with persistent or permanent AF were more than double than patients with paroxysmal AF. There were no differences between other neuropsychological parameters or vascular parameters in patients with different types of AF. Interestingly, in the ARIC (US-based Atherosclerosis Risk in Communities) study, which included 325 patients who had detailed cognitive tests and were monitored for heart rate for up to 14 days, only persistent AF and not paroxysmal AF is associated with modifying cognitive function. These findings suggest that maintaining AF over time can lead to changes in patients' cognitive function [41].

There have been studies that have shown that AF can lead to transient or chronic cerebral hypoperfusion by changes in heart rate, blood pressure, and cardiac output [42]. In one study, AF patients were divided by HR in those with low HR (< 50 bpm), medium (50-90 bpm) and high (> 90 bpm / min). In terms of cerebral hypoperfusion, low and high HR patients presented a higher risk of developing dementia than patients who presented medium HR. The effects of cerebral hypoperfusion due to AF association and heart failure may lead to an increase in cognitive impairment and dementia [43]. BP in large arteries at the base of the brain is considered to be greater than BP in the subcortical microvascularization. Cerebral perfusion occurs predominantly during diastole, so low diastolic pressures may increase the risk of small subcortical infarctions that could lead to the role of cognitive disorders [44].

If AF patients are at greater risk of dementia, it is very important to know and understand all the factors that determine the cognitive impairment in these patients with AF in order to intervene promptly and to prevent the complications of cognitive impairment in patients with this arrhythmia [45].

From all patients with AF, 9 (20%) patients were with $\text{CHA}_2\text{DS}_2\text{-VASc} < 3$ (1 or 2) and 36 (80%) patients with $\text{CHA}_2\text{DS}_2\text{-VASc} > 3$. MMSE and MOCA significantly decreased in patients with AF and $\text{CHA}_2\text{DS}_2\text{-VASc} < 3$ compared with patients with $\text{CHA}_2\text{DS}_2\text{-VASc} > 3$ ($p < 0.05$). ADL significantly decreased and GDS-15 significantly increased in patient with AF and $\text{CHA}_2\text{DS}_2\text{-VASc} > 3$ compared with patients with $\text{CHA}_2\text{DS}_2\text{-VASc} < 3$ ($p < 0.05$). It was found that the higher the $\text{CHA}_2\text{DS}_2\text{-VASc}$ score, the anticoagulation regimens should be carefully thought to prevent cognitive impairment [46, 47]. Old age is a very important risk factor for dementia, but also an important component in calculating the $\text{CHA}_2\text{DS}_2\text{-VASc}$ score [45]. Closer control of the risk factors included in the $\text{CHA}_2\text{DS}_2\text{-VASc}$ score could lead to good prevention of development disorders cognitive function in patients with AF. In the ARIC-NCS study, it was revealed that higher $\text{CHA}_2\text{DS}_2\text{-VASc}$ and HAS-BLED, HR, troponin T and higher LV mass index, male sex and low renal function were significantly associated with the occurrence of a higher number of MCI disorders or dementia [18].

In patients with AF, current guidelines recommend anticoagulant treatment to prevent stroke. Thus, using anticoagulant treatment should reduce the risk of cognitive impairment, with the risk of stroke decrease. [48] In our study, all patients with AF were with anticoagulants therapy. 21 patients were with OACs and 24 patients were with NOACs. From that 24 patients on NOACs, 9 (10%) were on apixaban therapy, 11 (12.2%) on dabigatran therapy and 4 (4.4%) on rivaroxaban therapy. A study involving 973 elderly AF patients after 33 months of follow-up found statistically insignificantly the occurrence of cognitive decline more severely in aspirin-treated patients than in warfarin-treated patients [49]. Particularly in patients who are at increased risk, e.g. patients who have a cognitive decline but not only, a better control of anticoagulant treatment could be particularly effective. In AF patients, understanding the mechanisms of production and accentuation of cognitive decline and dementia could identify more accurate prevention strategies [50]. Oral anticoagulation is a very important treatment for patients with AF [51]. Due to the hypercoagulable state of AF, applying an appropriate anticoagulant therapy can prevent or delay the development of cognitive impairment in AF patients [52]. In patients with AF, anticoagulation therapy may increase the risk of developing microbleeds, but also may increase the impact on existing ones, which has an effect on cognitive function [52].

In our study MMSE, MOCA and ADL significantly decreased in patients with AF and NOACs compared with patients with AF and OACs therapy ($p < 0.05$). One study found that patients using OACs had a higher prevalence and incidence of microbleeds. The risk of microbleeds was greater among the patients that showed greater variability in the control of anticoagulation [53]. In our study IMT and left ventricular parameters decrease but not statistically significant in a patient with OACs versus NOACs therapy. The association between AF and MCI can be due to the relatively frequent presence of microbleeds that can lead to cerebral hemorrhage, lacunar infarcts, and cerebral neurodegenerative changes [54]. The use of NOACs would be good for the management of risk factors, as the prognosis of stroke associated with AF is greater than stroke in non-AF patients [55]. Cognitive decline is associated

with SCI, and patients with AF have higher rates of SCI than patients without AF. The impact of anticoagulation on SCI remains unknown.

In a study, patients with OACs treatment who had a low percentage of maintenance within the optimal therapeutic range, had a higher risk of developing dementia, due to their long period of time when they were out of the optimal interval coagulation. There is currently insufficient data to prove that inappropriate anticoagulation may be involved in the development of cognitive impairment and dementia. We cannot prove whether a person with MCI when is diagnosed with AF and is being administered anticoagulant treatment, it may increase the risk of dementia [51].

A recent analysis of the risk of dementia in patients diagnosed with AF who received warfarin or non-vitamin K oral anticoagulants (NOAC) showed that there is a lower risk of dementia among patients receiving NOAC than those who received warfarin [51]. To date, there is insufficient evidence of anticoagulant treatment and its effect on the development of cognitive impairment, there are ongoing clinical trials that take into account the effectiveness of anticoagulation and the improvement of the quality of anticoagulation [51, 56].

Some studies have shown that dietary intervention and more adequate BP control can prevent AF, but it is not known yet whether these measures could reduce the risk of cognitive decline and dementia [57, 58].

Conclusions

It is important to know that cognitive decline occurs more frequently in patients with AF than those without AF, due to the association of cognitive decline with fibrillation, atherosclerosis, age or other cardiovascular risk factors. The more we manage to get better control of cardiovascular risk factors, to prevent cardiovascular disease, atherosclerosis, and to treat AF properly, we can basically prevent cognitive impairment in patients with AF. Dementia is a very important disease with psycho-social impact, so it is important to recognize it from the earliest signs and to act in a timely manner so that it can be avoided. In the future, from clinical trials are needed as much information as possible about the link between anticoagulation and cognitive decline in patients with AF to try to identify the first signs of cognitive decline and to prevent them from evolution.

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