

Clinical and Biological Profile of Patients with Non-Valvular Atrial Fibrillation and Hemodynamic Significant Valvular Heart Disease

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The non-valvular AF, beyond the guidelines, include 2 types of patients. We aimed to analyze the clinical and biological profile of patients with non-valvular atrial fibrillation (AF) and hemodynamic significant valvular heart disease. We included retrospectively 513 patients admitted in our hospital with non-valvular AF, and we divided into: study group (333 patients; 64.9%) and control group (180 patients; 35.1%) hemodynamic significant valvular heart disease. From the studied group 5.5% of patients associated all four valvular heart disease, 26.7% of patients associated mitral, aortic and tricuspid regurgitation and 71.9% of patients associated two valvular heart disease: 32.7% with mitral and aortic, 31.4% with mitral and tricuspid, 4.5% with tricuspid and pulmonary, and 3.3% with tricuspid and aortic. Dyslipidemia (higher cholesterol and trygliceride levels) was present in 14.5% of patients, statistic significantly more frequently in patients from the control group (11.4% vs 18.3%, $P = 0.033$). Dyslipidemia showed a significantly higher estimated risk for AF ($RR = 1.25$; $IC95\%: 0.99-1.56$), as well as diabetes mellitus ($RR = 1.36$; $IC95\%: 1.12-1.64$) and coronary heart disease ($RR = 3.70$; $IC95\%: 1.83-7.46$). Therefore patients with non-valvular AF and hemodynamic significant valvular heart disease, beyond the current guidelines, could have a completely different profile and prognosis.

Keywords: Atrial Fibrillation; Non-valvular; Valve Disease; Hemodynamically Significant; dyslipidemia

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population, and its prevalence is estimated to double in the next 50 years as the population ages [1-3].

Due to the predominance of degenerative etiology, the most common valvulopathies are aortic stenosis (AS) and mitral regurgitation (MR), while aortic regurgitation (AR) and mitral stenosis (MS) are less common [3,4]. Mitral valvulopathies (stenosis and regurgitation) significantly increase the risk of AF, which generates favorable conditions for thrombogenesis [5-8]. The meaning of valvular AF (or non-valvular) is far from clear to cardiologists and internists who deal with AF [11]. In patients with non-valvular AF thromboembolic risk assessment is based on CHA₂DS₂-VASc score [12,13]. The objective of the study was to find the clinical and biological profile of patients with non-valvular AF and hemodynamic significant valvular heart disease beyond the guidelines definition of valvular AF [9,10].

Experimental part

Patients and data collection

In this retrospective observational study we included all patients admitted in our hospital during 6 months, with non-valvular AF.

Valvular AF was defined as AF associated with rheumatic mitral stenosis and valvular prostheses (mechanical or bioprosthetic) or mitral valve repair (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty) [1,9,10].

The *inclusion criteria* were: patients older than 18 years, with documented non-valvular AF (associated or not with

hemodynamic significant valve disease, but which does not meet the criteria for valvular AF defined by the current guidelines [1,9,10], referred to our hospital, regardless of arrhythmia type: paroxysmal, persistent or permanent.

The *exclusion criteria* were: patients with valvular AF; patients with major contraindications to oral anticoagulation; patients with chronic kidney disease with creatinine clearance < 30 mL/min, pacemaker or automatic implantable cardioverter-defibrillator, hyperthyroidia, neoplasia.

The patients with non-valvular AF included in the study was divided into two groups depending on the presence of significant hemodynamic valvular heart disease: the study group- patients with significant hemodynamic valvular heart disease (mitral, aortic, tricuspid or pulmonary regurgitation II-IV degree; mild/moderate/severe aortic stenosis) and the control group- patients without significant hemodynamic valvular heart disease. Non-valvular AF was documented by standard ECG in 12 leads and/or 24 h ECG Holter monitoring.

After a detailed medical history the following clinical parameters were noted: age, sex, smoker status, obesity (defined as body mass index - BMI - higher than 30 kg/m²), comorbidities (dyslipidemia, hypertension, aortic atheroma plaques, diabetes mellitus, heart failure, ischemic heart disease and peripheral arterial disease).

Laboratory measurements

All laboratory measurements were performed on fasting blood samples. The biological tests evaluated were: total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglyceride,

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alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood glucose, creatinine, C reactive protein (CRP), thyroid stimulating hormone (TSH).

Echocardiography measurements

Echocardiographic measurements were assessed by bidimensional transthoracic echocardiography with an Acuson Sequoia 256 Ultrasound Machine (Siemens). All patients underwent standardized transthoracic two-dimensional echocardiography evaluation. The echocardiographic parameters assessed during hospitalization were related to valvular morphology and function. In patients eligible for the study valvular regurgitation was scored from 0 through 5: 0 = no regurgitation, 1 = mild, 2 = mild-moderate, 3 = moderate, 4 = severe. Grades 2-4 were considered significant. Similarly, stenosis severity was assessed as: 0 = no stenosis, 1 = mild stenosis, 2 = moderate stenosis, 3 = severe stenosis. For aortic valve, all degree of severity were considered hemodynamically significant. In accordance with the inclusion criteria, only mitral stenosis patients were included in the study.

This study has been performed in compliance with the ethical principles of the hospital and University Ethics Committee. Informed consent was obtained from each patient before the inclusion in the study. This study conforms to the Declaration of Helsinki.

Statistical analysis

Normal distribution of variables was evaluated using the Kolmogorov-Smirnov test. Categorical data are presented as frequencies and percentages; continuous variables are expressed as mean \pm standard deviation. We use for the statistical evaluation the following tests: ANOVA test consisted in analyzing the dispersion of the dependent variable: intro and intergroup, the coefficient of variation (CV%), the t-Student test, the Kruskal-Wallis correlation and the Pearson (r) coefficient. All statistical tests were two-tailed and performed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was set as statistical significance.

Results and discussions

We included 513 consecutive patients with mean age of 69.33 ± 10.23 years in the study: 48.9% with permanent AF, 16% with persistent AF, and 35.1% with paroxysmal AF. Almost two third of patients (333 patients; 64.9%) were included in the study group (AF and significant hemodynamic valvular heart disease) and one third (180 patients; 35.1%) in the control group (AF without significant hemodynamic valvular heart disease).

Clinical parameters

Demographic and valve disease distribution in the study population are shown in table 1.

The most frequent valvular heart disease was MR (75%), and moderate degree was most frequently reported (32.2%). Tricuspid regurgitation was noted in 67.6% of patients, particularly with moderate degree (35.9%). Twenty eight patients (5.5%) associated all valve disease (mitral, aortic, tricuspid and pulmonary), 137 patients

Table 1
DEMOGRAPHIC PARAMETERS AND VALVULAR HEART DISEASE DISTRIBUTION IN THE STUDY POPULATION

PARAMETER	N (%)
Mean age (mean \pm SD), years	69.3 \pm 10.2
Men, n (%)	290 (56.5)
Smokers, n (%)	111 (21.6)
Alcohol consumers, n (%)	64 (12.5)
Mitral regurgitation	
II degree, n (%)	165 (32.2)
III degree, n (%)	62 (12.1)
IV degree, n (%)	9 (1.8)
Aortic regurgitation	
II degree, n (%)	76 (14.8)
III degree, n (%)	13 (2.5)
Tricuspid regurgitation	
II degree, n (%)	184 (35.9)
III degree, n (%)	56 (10.9)
IV degree, n (%)	5 (1.0)
Pulmonary regurgitation	
I degree, n (%)	45 (8.7)
II degree, n (%)	12 (2.3)

(26.7%) associated MR, AR and TR and 369 patients (71.9%) associated two valve regurgitation.

The patients from the study group were statistically significant older than 70 years, less often smokers and obese (table 2).

Distribution by age group revealed that the majority of patients from the study group (42%) was in decade 70-79 years, while the majority of patients from the control group (40%) was in decade 60-69 years (*P*=0.001). The percentage of patients with valvular heart disease was significantly higher in older age (Chi-square=30,54; *df*=5; *P*=0.001).

The gender distribution was relatively homogeneous; male patients were more frequent in the both groups. The evaluation of cardiovascular risk factors (as shown in table 3) showed that arterial hypertension was present in 61.5% of patients, without significant differences in the study group (59.8% vs 56.7%, *P* = 0.498). Diabetes mellitus was in 21.3% of the patients, being significantly more common in patients from the control group (31.1% vs 17.4%, *P* = 0.011).

Dyslipidemia was present in 14.5% of patients, statistically significantly more frequently in patients from the control group (11.4% vs 18.3%, *P*= 0.033). Diabetes mellitus (RR = 1.36; IC95%: 1.12-1.64), dyslipidemia (RR=1.25; IC95%: 0.99-1.56) and coronary heart disease (RR = 3.70; IC95%:

Table 2
DEMOGRAPHIC PARAMETERS OF THE STUDY SUBGROUPS

	TOTAL		PARAMETERS									
	N	%	Men	%	≥ 70 years	%	Smoker	%	Alcohol	%	Obesity	%
STUDY GROUP	333	64.9	178	53.5	203	61.0	63	18.9	36	10.8	71	21.3
CONTROL GROUP	180	35.1	112	62.2	68	37.8	48	26.7	28	15.6	57	31.7
Chi2 test (p value)			0.069		0.001		0.044		0.126		0.050	

Table 3
CLINICAL PARAMETERS OF THE STUDY GROUPS AND RELATIVE RISK FOR ATRIAL FIBRILLATION

COMORBIDITY	STUDY GROUP N=333	CONTROL GROUP N=180			RELATIVE RISK FOR ATRIAL FIBRILLATION		
	n	n	CHI ²	P	OR	RR	IC95%
Hypertension, n (%)	199 (59.8)	102(56.7)	0.46	0.498	1.05	0.96	0.84-1.27
DM, n (%)	58 (17.4)	56 (31.1)	12.3	0.001	0.56	1.36	1.12-1.64
Dyslipidemia, n (%)	38 (11.4)	33 (18.3)	4.55	0.033	0.62	1.25	0.99-1.56
CHD, n (%)	11 (3.3)	22 (12.2)	14,0	0.001	0,25	3,70	1,83-7,46
Apnea/COPD, n (%)	27 (8.1)	17 (9.4)	0.26	0.608	0.86	1.06	0.83-1.36
Anemia, n (%)	6 (1.8)	1 (0.6)	1.56	0.212	3.00	0.75	0.55-1.03
VA, n (%)	9 (2.7)	2 (1.1)	1.55	0.214	0.56	0.79	0.59-1.05
Stroke/TIA, n (%)	7 (2.1)	5 (2.8)	0.23	0.633	0.70	1.12	0.69-1.81
Hyperthyroidism, n (%)	12 (3.6)	6 (3.3)	0.03	0.873	0.98	0.97	0.70-1.36
Hypothyroidism, n (%)	17 (5.1)	16 (8.9)	2.67	0.102	0.57	1.28	0.91-1.79

CHD: coronary heart disease; DM: diabetes mellitus; TIA: transient ischemic attack; VA: ventricular arrhythmias.

Table 4
BIOLOGICAL PARAMETERS OF THE STUDY SUBGROUPS: I = STUDY GROUP, II = CONTROL GROUP

PARAMETER	Group	N	Average	Standard deviation	Confidence Interval 95%	Test F (ANOVA) p
Cholesterol (mg/dL)	I	323	172.61	42.42	167.97	0.008
	II	168	183.93	49.06	176.46	
LDL-Cholesterol (mg/dL)	I	316	104.62	33.04	100.96	0.098
	II	165	110.43	42.27	103.93	
HDL-Cholesterol (mg/dL)	I	321	47.52	14.42	45.94	0.075
	II	167	50.22	18.31	47.42	
Trygliceride (mg/dL)	I	322	104.80	58.16	98.42	0.032
	II	168	116.68	58.15	107.83	
Thyroid Stimulating Hormon (UI/mL)	I	23	2.44	2.81	1.22	0.692
	II	12	3.02	5.84	-0.69	
C Reactive Protein (mg/dL)	I	158	29.30	45.71	22.11	0.503
	II	76	25.08	43.60	15.12	
Serum creatinine (mg/dL)	I	329	1.19	0.53	1.13	0.499
	II	178	1.15	0.58	1.07	

HDL: high density lipoprotein; LDL: low density lipoprotein.

1.83-7.46) showed a significantly higher estimated risk for AF (as shown in table 3).

Biological parameters

Blood tests (shown Table 4) showed elevated cholesterol and trygliceride levels in patients from control group, while for LDL-cholesterol, HDL-cholesterol, thyroid stimulating hormone, C reactive protein and creatinine values did not.

Mean value of CHA2DS2-VASc and HAS-BLED was 3.05 ± 1.54 and 2.38 ± 0.97 , respectively. Mean CHA2DS2-VASc and HAS-BLED score value were significantly higher in the study group: 3.19 vs. 2.79; $P = 0.006$, and 2.44 vs 2.27; $P = 0.05$, respectively. In this study, 82% of patients have had CHA2DS2VASc score ≥ 2 ; only 52% of these patients received appropriate anticoagulation treatment.

A slightly higher estimated risk of valve disease was noted in patients who associated: hypercholesterolaemia (RR = 1.25, IC95%: 0.99-1.56), hypertriglyceridaemia (RR = 1.30, IC95%: 0.45-3.47) and right bundle branch block (RR = 1.21; IC95%: 0.42-1.37).

Patients with non-valvular AF, left-sided valve disease (excluding mitral stenosis and prostheses) have a higher CHA2DS2VASc score [15]. Therefore, patients with non-valvular AF seems to be a heterogenous group of patients with possible clinical significantly different from those without hemodynamic significant valvular heart disease. The profile of these patients is shown in table 6. They are older, with less comorbidity like obesity and chronic coronary disease, higher thromboembolic and hemoragic risk. The last ones could mean a worse prognosis for these patients.

Diabetes mellitus and dyslipidemia were statistically significant more frequent in patients from the control group. In these patients we found a significantly higher estimated risk for AF.

In clinical practice in patients with non-valvular AF is mandatory to assess thromboembolic risk score by CHA2DS2VASc. Patients with CHA2DS2VASc score 0 have an annual risk of thromboembolic events not 0. This might be due to the heterogeneity of non-valvular AF patients and hemodynamic significant valvular heart disease (other

PARAMETER	Study group (N=333)	Control group (N=180)	P
Age ≥ 70 years (%)	61.0	37.8	0.001
Smoker (%)	18.9	26.7	0.044
Diabetes Mellitus (%)	17.4	31.1	0.001
Dyslipidemia (%)	11.4	18.3	0.033
Chronic Coronary Disease (%)	3.3	12.2	0.001
Mean CHA ₂ DS ₂ -VASc	3.19±1.53	2.79±1.52	0.006
Mean HAS-BLED	2.44±0.95	2.27±0.99	0.05

SD: standard deviation

than those with valvular prosthesis or rheumatic mitral valve disease) [16, 17].

Limitations

This study has the limitations of an observational retrospective analysis with many variables which were analysed. In this there was a control group.

Conclusions

In patients with non-valvular AF and hemodynamic significant valvular heart disease, dyslipidemia showed a significantly higher estimated risk for AF, as well as diabetes mellitus and coronary heart disease. Therefore these patients, beyond the current guidelines, could have a completely different profile and prognosis.

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Table 5
CLINICAL PROFILE OF PATIENTS WITH
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