Clinical Profile of Patients with Atrial Fibrillation According to EHRA (Evaluated Heart Valves, Rheumatic or Artificial) Categorization in A Middle-Income Country

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ABSTRACT

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. As of 2017, a functional EHRA (Evaluated Heart valves, Rheumatic or Artificial) categorization was proposed to replace the terms valvular and non-valvular AF. In our country, despite the incidence of rheumatic valve heart disease, studies on this new categorization are scarce. Objective: to assess the clinical profile of patients (pts) with AF, using the EHRA categorization as a parameter. Methods: this is a prospective, observational and cross-sectional study with 475 pts with AF from a university institution. Clinical and laboratory evaluations were carried out, as well as the calculation of risk scores for embolism, bleeding and renal function. Statistical analysis was performed by non-parametric tests, in addition to the chi-square test. Results: the pts were divided into 3 groups, according to the EHRA categorization: EHRA 1, with 144 pts, with mitral stenosis or mechanical prosthesis; EHRA 2, with 46 pts with other valvular heart diseases; and EHRA 3, with 285 pts, without valvular heart disease. Mean ages were 51.5; 57.6 and 62.9 years, respectively ($p < 0.0001$). The proportions of women were 75%; 52.1% and 40.7% ($p < 0.0001$). The presentation of the AF was permanent in 68.1%; 60.9%; 52.3% of pts ($p = 0.008$) and 86.0%; 47.8% and 53.3% of pts were using oral anticoagulants, respectively ($p < 0.0001$). The means of left ventricular ejection fraction were 0.58; 0.57 and 0.46; of left atrium were 55.9; 52.5 and 48.1 mm; ATRIA score of 1.4; 1.3 and 2.1; and the glomerular filtration rate of 91.7; 91.1 and 75.0 mL/min/1.73m², respectively ($p < 0.0001$). There was no difference among groups regarding blood pressure and heart rate at study entry and regarding the history of embolism. Conclusions: pts from the EHRA 1 categorization were younger, with a higher proportion of women, permanent AF and use of oral anticoagulants. Systolic dysfunction predominated in those without valve disease, who also had a higher bleeding score and greater impairment of renal function.

Keywords: Anticoagulation, atrial fibrillation, glomerular filtration rate, mechanical prosthetic heart valves, risk assessment, thromboembolism.

Published Online: January 24, 2022

ISSN: 2736-5476

DOI: 10.24018/ejclinmed.2022.3.1.161

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I. INTRODUCTION

In 2017, a functional EHRA (Evaluated Heart valves, Rheumatic or Artificial) categorization was proposed due to heterogeneity of the definition of valvular and non-valvular atrial fibrillation (AF) [1]. Epidemiological data demonstrate that there has been an increased incidence of degenerative etiology in valvular heart disease in high-income countries. On the other hand, rheumatic etiology is still the main cause

of valvular heart disease in low- or middle-income countries, with a great impact on patient morbidity and mortality, especially if associated with AF [2]-[4]. In rheumatic heart valve disease, the prevalence of AF can reach 80% [5]. Therefore, vitamin K antagonist oral anticoagulants are indicated to prevent thromboembolic events in patients with moderate to severe mitral stenosis and AF, while direct oral anticoagulants are contraindicated [3]. This scenario reflects the importance of that categorization for the practical use of

the type of oral anticoagulation based on scientific evidence.

There are differences in the burden of rheumatic heart disease. In some countries, there is a decrease in new cases, but with a predominance of chronic presentation of this rheumatic valve disease. Due to the difficulty in accessing medical care in some regions and poor adherence to prevention, there is an unfavorable impact on the clinical evolution and surgical outcomes of these patients [6].

In our country, despite the incidence of rheumatic heart valve disease, studies are scarce about this new categorization. Thus, this study aims to evaluate and compare the clinical profile of patients with AF, according to the EHRA type 1 and type 2 categorization, and patients with AF and without valvular heart disease.

II. METHODS

A. Participants and Study Procedure

This is a prospective, observational and cross-sectional study with AF patients over 18 years of age undergoing clinical follow-up at an academic medical center in a middle-income country. The study was done between May 2018 and March 2020. These patients were divided into three groups as follows:

- Group 1: EHRA Type 1, which refers to AF patients with mitral stenosis (moderate to severe, of rheumatic origin) or with mechanical replacement of the prosthetic valve;
- Group 2: EHRA Type 2, which refers to AF patients with other valvular heart diseases or with biological prosthetic valves without dysfunction implanted more than three months ago;
- Group 3: patients without valve diseases or mechanical or biological prosthetic valves.

The patients underwent clinical evaluation and laboratory tests (electrocardiogram, echocardiogram and blood tests). Risk scores for embolism (for groups 2 and 3) and for bleeding (for all groups) were taken at study entry through data collected from medical records. Baseline renal function was calculated for all patients. The calculated embolism scores were CHA₂DS₂-VASc and CHA₂DS₂-VASc-RAF. The calculated bleeding score was ATRIA. For renal function, creatinine clearance by the Cockcroft-Gault formula (CG) and glomerular filtration rate by the Diet Modification in Kidney Disease (MDRD) equation were used.

B. Ethical Aspects

Before the start of the study, participants were informed about the research and procedures. All patients gave written informed consent. The study protocol complies with ethical guidelines and was approved by the institution's human research committee.

C. Statistical Analysis

Statistical analysis was performed using SPSS Statistical Software, Version 16.0 (SPSS Inc, Chicago, IL, USA). Categorical variables were expressed as frequency (percentage) and compared with the chi square test or Fisher's exact test as appropriate. Continuous data are presented as mean $\pm$ standard deviation or median and interquartile range, as appropriate. The Kruskal-Wallis test or ANOVA test was

used for comparison among the three groups. Comparison between continuous variables of two groups was performed using the Mann-Whitney test. The normality assumption was verified by Shapiro-Wilk test. All values were two-tailed, and a P value < 0.05 was considered statistically significant.

III. RESULTS

A. Patient Baseline Characteristics

A total of 475 AF patients were enrolled. The mean age was 59.0 ± 14.8 years, ranging from 18 to 92 years of age. 52.2% of the patients were female. The median left ventricle ejection fraction was 0.56 (interquartile range 0.37 - 0.65), ranging from 0.12 to 0.85.

B. Comparison among Groups

The comparison among the three groups is shown in Table I and in Fig. 1.

TABLE I: COMPARISON BETWEEN GROUPS REGARDING CLINICAL AND LABORATORY VARIABLES AND EMBOLISM AND BLEEDING SCORES

Variables/scores	Group 1 (n=144)	Group 2 (n=46)	Group 3 (n=285)	p-value
Mean age (years)	51.7	57.6	62.9	<0.0001
Females (%)	75.0	52.1	40.7	<0.0001
BMI (Kg/m ²)	25.3	24.6	24.6	0.59
Permanent AF (%)	68.1	60.9	52.3	0.008
Previous systemic embolism (%)	25.6	10.8	22.5	0.16
Baseline HR	80	79.5	76	0.81
Baseline BP	113/70	116/76	120/70	0.21
LV diastolic diameter (mm)	49.0	53.5	57.0	<0.0001
LV systolic diameter	32.0	35.0	43.0	<0.0001
LA diameter	55.0	53.0	48.0	<0.0001
EF	0.61	0.62	0.48	<0.0001
In use of OC (%)	86.1	47.8	53.3	<0.0001
CHA ₂ DS ₂ -VASc		2.02	3.02	0.001
CHA ₂ DS ₂ -VASc-RAF		9.67	10.17	0.20
CG	76.6	73.1	54.7	<0.0001
MDRD	88.7	82.8	72.4	<0.0001
ATRIA	1.43	1.36	2.16	<0.0001

BMI: body mass index (median); AF: atrial fibrillation; HR: heart rate (median - bpm); BP: blood pressure (median - mmHg); diameter in mm (median); LV: left ventricle; LA: left atrium; EF: ejection fraction (median); OC: oral anticoagulant; CG: creatinine clearance (median - mg/dL); MDRD: glomerular filtration rate by the Diet Modification in Kidney Disease (median - mL/min/1.73 m²).

Fifteen patients had mechanical prosthetic valves in group 1; 13 in the mitral position and 2 in the aortic position. The other patients in group 1 had moderate to severe mitral stenosis. The main etiologies of heart disease in patients in group 3 were hypertensive (36.8%), dilated cardiomyopathy of different etiologies, mainly of ischemic etiology (53%), and other etiologies without left ventricular systolic dysfunction, such as coronary artery disease, congenital heart disease, brady-tachycardia syndrome.

The Canadian Cardiovascular Society (CCS) AF Severity Scale, which describes the severity of symptoms related to AF, was similar among the three groups (2.6; 2.6 and 2.8 for groups 1, 2 and 3, respectively, p=0.97).

Regarding the use of oral anticoagulants, 298 patients were using vitamin K antagonists, nine were using rivaroxaban, eight were using apixaban and two were using edoxaban. No patient was using dabigatran at the time of study entry. The oral anticoagulant used by patients in group 1 was warfarin.

Sixty-five patients (13.7%) used a pacemaker in VVI mode. The proportion of patients with cardiac pacemakers was 4.7%; 8.7% and 18.9% in groups 1, 2 and 3, respectively ($p<0.0001$).

Fig. 1. Number of patients in each group according to AF presentation.

IV. DISCUSSION

The major findings of this study are that patients in group 1 (EHRA type 1) were younger, had a higher proportion of permanent AF and a higher frequency of warfarin use, demonstrating agreement with the literature. On the other hand, older patients had a low proportion of oral anticoagulant use despite higher scores for systemic embolism.

The main etiology of mitral stenosis is rheumatic fever, especially in developing countries. There is a predominance of this valvular heart disease in females [3],[7]- [9]. Thus, the greater proportion of women in group 1 in this study is in line with the literature as well as age. Rheumatic valvular heart disease affects more young people, unlike the degenerative etiology that affects older patients [7]-[10].

AF is a very common arrhythmia, with an increase in prevalence with age. Its risk is 4.98 in those aged between 60 and 69 years, and 9.39 in those aged 80 to 89 years, compared to the risk in those aged 50 to 59 years [11]. In patients with rheumatic heart disease, its prevalence can reach 80%, with an average of almost 33% [5]. A recent study of patients with AF rhythm and bioprosthetic valve demonstrated that AF was paroxysmal, persistent, or permanent in 36.9%, 34.6%, and 28.5% of patients, respectively [12]. And in large registries of heart failure, the prevalence of AF ranges from 23.0 to 33.7% in patients with preserved ejection fraction, and it ranges from 32 to 39% in those with reduced ejection fraction [13]. Structural and inflammatory changes in the left atrium and the increase in its pressure due to mitral valve involvement predispose to the rhythm of AF, which explains the higher proportion of permanent AF in group 1. This is corroborated by the greater diameter of the left atrium in this group, with a statistically significant difference.

The association between AF and systemic embolism, including stroke, is well established. Therefore, the indication of oral anticoagulation is imperative. Direct anticoagulants are indicated for the prevention of systemic embolism in patients with non-valvular AF with a CHA₂DS₂-VASc score ≥ 2 . Its use is also acceptable in patients with AF undergoing valve bioprosthetic surgery after more than 3 months. They can be used in those patients with AF and valvular heart disease, except for moderate to severe mitral stenosis and

patients with mechanical replacement of the prosthetic valve. Thus, for this group of patients (EHRA Type 1), vitamin K antagonists should be used to prevent thromboembolism [3], [14], [15]. In the present study, the systemic embolism rate reached up to 25.3%, with no difference among groups. Literature data indicated that the most important morbidity in patients with AF is stroke, which is associated with this arrhythmia in up to 25% of the time, but AF may be responsible for 43.9% of disabling or fatal strokes [16].

There are few studies with functional EHRA (Evaluated Heart valves, Rheumatic or Artificial) categorization. Nationwide cohort study with a large sample of patients with valvular heart disease and AF, but with 90% of patients with EHRA type 2, demonstrated a rate of 14.6% and 18.6% of thromboembolism in patients with EHRA type 1 and EHRA type 2, respectively [17]. A study from the same group showed that the rate of previous thromboembolism ranged from 10.0% to 14.6% between patients in both groups [18]. The higher rate of thromboembolism in our study can be explained by the higher proportion of patients with moderate to severe mitral stenosis in group 1, which was 89.5%, compared to the rate of 29.2% in the study mentioned above.

The underutilization of oral anticoagulation is still a current fact. In low- and middle-income countries, the oral anticoagulation rate ranges from 11% to 85%, and in Latin America the average rate is 43.3% [19]. With regard to the use of warfarin, this occurs mainly in elderly people aged at least 75 years, with higher CHA₂DS₂-VASc score, even in developed countries, with a prescription rate of 50.8%, and anemia is one of the associated independent factors [20]. This rate of warfarin use is similar to that of group 3 in our study, which consisted of older patients without mitral valve disease. In addition, this group also had a higher ATRIA score, which may have influenced the management of oral anticoagulant use. Another factor that may have interfered is renal function, which also showed greater impairment in group 3. Despite the increased risk of stroke in patients with AF and chronic kidney disease, there is an increased risk of bleeding with the use of oral anticoagulants. This risk is greater in patients with end-stage renal disease, in whom the use of warfarin showed a neutral effect on ischemic stroke and increased bleeding and hemorrhagic stroke [21].

Due to the importance of renal function in patients with

AF, a cross-sectional study validated by another demonstrated that AF type (persistent and permanent AF) and renal dysfunction (defined as glomerular filtration rate $<56 \text{ mL/min/1.73 m}^2$) were independent predictors of thrombus in the left atrium [22], [23]. Thus, the CHA2DS2-VASc-RAF score showed better performance which motivated us to calculate this score for our population. However, in the literature there is no comparison between patients with EHRA type 2 and those with non-valvular AF regarding this score.

The high anticoagulation rate in group 1 of this study is also similar to the recent published study, in which the rates were 62.5% for patients with moderate to severe mitral stenosis and 100% for those with mechanical replacement of the prosthetic valve [18]. On the other hand, the anticoagulation rate in group 2 was lower than in the aforementioned study, which showed rates between 50.8% and 67.1% for patients in the EHRA type 2 categorization.

Direct oral anticoagulant therapy for AF-related stroke prevention was underutilized in this study. A recently published national registry of 1423 patients with AF and with at least one thromboembolic risk factor in upper-middle-income country demonstrated that 34.6% were using direct oral anticoagulants [24]. Our study was carried out with patients from a university hospital, whose care is provided to those from the national public health system, excluding the care of patients from the private health system. There is no direct oral anticoagulant supply. Therefore, these factors explain the low percentage (6%) of the use of these direct anticoagulants in relation to the total number of patients under oral anticoagulation.

Regarding the proportion of patients with pacemakers, the results of this study are in accordance with the main indications for pacemaker implantation, since the highest proportion occurred in group 3. These indications are sinus node disease and advanced atrioventricular block, conduction disorders that occur in older patients and patients with cardiomyopathy [25], [26]. In the study that compared EHRA type 1 and EHRA type 2 patients, the proportions of patients with pacemakers were up to 12.1% and 11.3%, respectively.

V. LIMITATIONS

The main limitations of this study are the sample size and patient selection bias, since the study was carried out in a single center. The quality of oral anticoagulation using the international normalized ratio (INR) to verify the time in therapeutic range was not measured because it is a cross-sectional study.

VI. CONCLUSIONS

Patients in the EHRA 1 categorization were younger, with a higher proportion of women, predominant presentation of permanent AF and a higher frequency of oral anticoagulant use.

Systolic dysfunction was more present in those patients without valvular heart disease (group 3), who also had a higher bleeding score and greater impairment of renal function.

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