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ORIGINAL ARTICLE

# Evolution of Patients With Atrial Fibrillation According to the EHRA Categorization

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## Abstract

**Background:** The lifetime risk of developing Atrial Fibrillation (AF) is one in three adults, with a prevalence ranging from 2% to 4%. In 2017, the Evaluated Heart valves, Rheumatic or Artificial (EHRA) classification was introduced to guide oral anticoagulation (OAC) for patients with AF and valvular heart disease.

Objective: To analyze the evolution of patients with AF according to the EHRA categorization type 1, type 2, and those without valvular heart disease (group 3).

**Method:** Prospective, observational, and longitudinal study with 421 patients with AF, divided into three groups. Baseline risk scores for embolism, bleeding, and OAC quality were calculated. Events were verified during the 12-month clinical follow-up. Chi-square, parametric, and non-parametric tests were used for statistical analysis, in addition to the Kaplan-Meier curve. P-value < 0.05 was the statistical significance criterion.

**Results:** The average age was 58.6 years; 227 patients were women and 269 had OAC. There were 113 OAC EHRA type 1 patients, 53 type 2, and 255 patients from group 3. Age was lower, the proportion of women and OAC usage was higher in group 1 and there was a lower ejection fraction in group 3. During follow-up, the OAC percentage was 87.6% in type 1; 62.2% in type 2; and 56.0% in group 3 ($p < 0.0001$), with no difference regarding OAC quality, bleeding rate, embolism, or combined events. A higher total mortality rate was observed in group 3 ($p = 0.02$).

**Conclusion:** Despite the higher use of OAC in EHRA type 1, there were no differences between the groups regarding bleeding, embolism, or combined events. Group 3, characterized by greater systolic dysfunction, exhibited higher total mortality rates.

**Keywords:** Atrial Fibrillation; Heart Valve Diseases; Clinical Evolution; Mortality.

## Introduction

The lifetime risk of developing Atrial Fibrillation (AF) stands at one in three adults, typically beginning at age 55, resulting in a prevalence ranging from 2% to 4%.[1] Global burden data from 2020 showed a prevalence of 766 to 876 per 100,000 individuals in most of Brazil, with an annual mortality rate in South America at 17%, nearly double that of North America.[2]

Risk factors influencing the onset, progression, and recurrence of AF include non-modifiable factors such as age, genetic predisposition, and ethnicity (with limitations due to specific study populations), as well as potentially modifiable factors like obesity, sedentary lifestyle, diabetes, hypertension, heart failure, coronary artery disease, valvular heart disease, dyslipidemia, sleep apnea, chronic kidney disease, smoking, alcohol consumption, and others such as air quality, post-operative status, and SARS-CoV-2 infection.[1,3-5]

The terms valvular and non-valvular AF should not differentiate AF associated with moderate to severe Mitral Stenosis (MS) or mechanical valve prostheses from other AF patients.[1] Therefore, a 2017 proposal introduced the Evaluated Heart valves, Rheumatic or Artificial (EHRA) functional categorization for determining oral anticoagulation (OAC) use in AF patients with valvular heart disease.[6] EHRA type 1 includes patients with moderate to severe MS

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**Central Illustration: Evolution of Patients With Atrial Fibrillation According to the EHRA Categorization**

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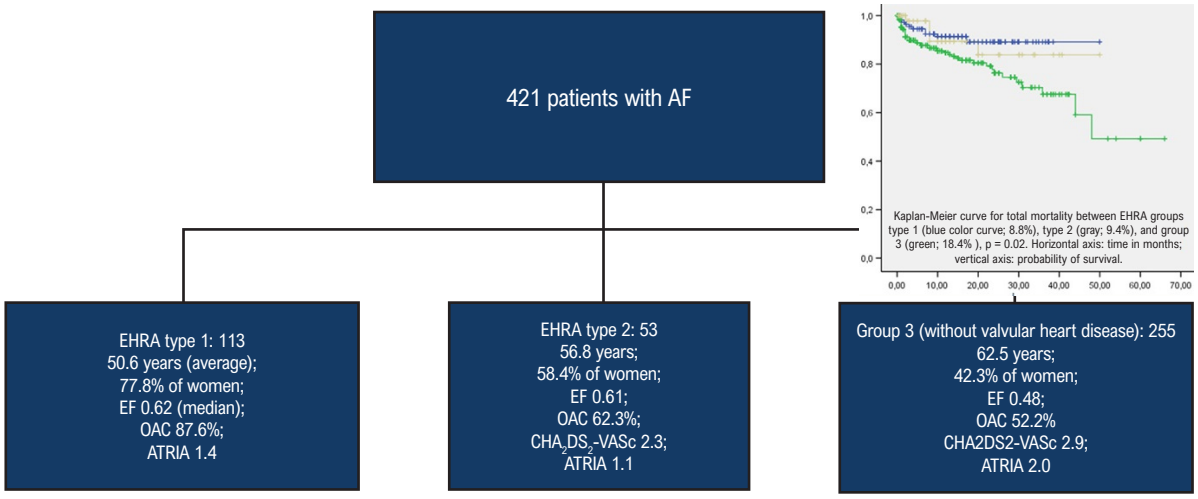


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*AF: Atrial Fibrillation; EHRA: Evaluated Heart valves, Rheumatic or Artificial; EF: Ejection fraction; OAC: oral anticoagulation.*

or mechanical valve prostheses, while EHRA type 2 encompasses those with other valve diseases or biological valve prostheses implanted over three months ago.

Studies on this categorization have shown its utility in predicting thromboembolic events and bleeding risks in both EHRA type 1 and type 2 groups. They also highlight a significant risk of systemic embolism even in EHRA type 2 patients under 65 years with only one comorbidity.[7-11] Despite increasing rates of rheumatic heart disease, the primary cause of MS in regions of low to medium socioeconomic development, including Brazil, there remains a lack of national studies on this categorization. Therefore, this study aims to investigate the outcomes of AF patients according to EHRA categorization.

## Method

### Population and study design

This is a single-center (conducted in a university hospital), prospective, observational, and longitudinal study with 421 participants (patients) with AF, aged ≥ 18 years, included after granting free and informed consent (FIC), in the period ranging from May 2018 to March 2020.[12,13] All patients underwent clinical and laboratory evaluation (including electrocardiogram, transthoracic echocardiogram, and clinical pathology tests) and clinical follow-up. The AF rate was documented using an electrocardiogram. Three groups were formed according to the EHRA categorization type 1, type 2, and group 3 of participants without primary valvular heart disease or mechanical or biological valve prostheses. Upon enrollment into the study, risk scores for embolism (for groups 2 and 3) and bleeding (for all groups) were calculated according to guidelines,[1,14] as well as renal function. For the severity of symptoms related to AF, the CCS [15] and EHRA[16] scales were employed. The scores used to estimate the occurrence of embolism were $CHA_2DS_2$-VASc[1,16] and $CHA_2DS_2$-VASc-RAF. To estimate bleeding[1,14] the HAS-BLED and ATRIA scores were used.

For patients taking warfarin, the quality of individual OAC was based on the percentage of time during which the International Normalized Ratio (INR) was maintained in the therapeutic range during the 6-month follow-up period. Clinically relevant and non-relevant bleeding resulting from OAC,[17] occurrences of systemic embolism, cardiac death, total mortality, and events (defined as the combination of all, including hospitalization) were considered during the median clinical follow-up of 12 months.

### Ethical aspects

The study was approved by the institution's Research Ethics Committee and all participants signed the informed consent form.

### Statistical analysis

Statistical analysis was performed using the SPSS software for Windows, version 16.0 (SPSS, Inc., Chicago, Illinois). Qualitative variables were presented using frequencies, and the continuous variables using mean and standard deviation (for variables with normal distribution), or median and interquartile ranges (for variables without normal distribution), according to the Kolmogorov-Smirnov test with Lilliefors correction. Comparison between groups was made using the ANOVA test (One-Way) or Student's T-test (unpaired) for continuous variables with normal distribution, or the Kruskal-Wallis test for variables with non-Gaussian distribution. The Tukey test (post hoc) and the Mann-Whitney test (with Bonferroni correction) were used to determine the differences between means and medians, respectively. The chi-square test was used for qualitative variables. The Kaplan-Meier curve was applied to compare the three groups regarding the occurrence of events (cardiovascular, embolism, bleeding) separately and combined and the Log-rank test was used. P-value $< 0.05$ was the statistical significance criterion.

## Results

### Baseline characteristics of the study population

The study included 421 patients, aged 58.6 ± 14.9 years (between 18 and 92 years) on average, 227 of whom were women. AF presentation at the time of entry into the study was permanent in 244, persistent in 66, and paroxysmal in 111. The median Left Ventricular Ejection Fraction (LVEF) was 0.56 (interquartile range – Q1-Q3: 0.37 – 0.65) and the mean Left Atrial (LA) diameter was 50.8 ± 9.4 mm (ranging from 30 to 84).

### Comparison between groups

According to the group's categorization, 113 patients were of the EHRA type 1, 53 of type 2 and group 3 consisted of 255 patients. Among the EHRA type 1 group, 15 patients had mechanical prostheses; 13 in the mitral position and 2 in the aortic position. The others had moderate to severe MS of rheumatic etiology. The primary etiologies of heart disease in group 3 included hypertension (39.6%), dilated cardiomyopathy of various causes, predominantly ischemic (45.5%), and other etiologies not associated with systolic dysfunction, such as coronary artery disease, congenital heart disease, and brady-tachycardia syndrome. Regarding the use of OAC, 258 patients were taking warfarin, 6 were taking rivaroxaban, 2 were taking apixaban, 2 were taking edoxaban, and 1 was taking dabigatran.

Table 1 shows the comparison between groups regarding clinical variables, laboratory data, and scores for embolism and bleeding at the beginning of the study. In the EHRA type 1 group, patients were younger, with a higher proportion of women and a greater percentage using OAC. Tukey test p-values for age were 0.019 between groups 1 and 2, < 0.0001 between groups 1 and 3, and 0.028 between groups 2 and 3. LA diameter comparisons revealed differences of 0.20 between groups 1 and 2, < 0.001 between groups 1 and 3, and 0.005 between groups 2 and 3, with group 3 exhibiting smaller diameters.

Group 3 had a larger left ventricular systolic diameter compared to group 1, and lower LVEF compared to groups 1 and 2. Mann-Whitney test p-values for left ventricular systolic diameter were 0.004 between groups 1 and 2, < 0.001 between groups 1 and 3, and 0.09 between groups 2 and 3. Regarding LVEF, the Mann-Whitney test p-values were 0.34 between groups 1 and 2, < 0.001 between groups 1 and 3, and 0.003 between groups 2 and 3. Group 3 showed a higher $CHA_2DS_2$-VASc score and ATRIA score (compared to other groups) and a lower glomerular filtration rate in relation to group 1. The p-values referring to the Tukey test regarding the ATRIA score were 0.74 between groups 1 and 2, 0.015 between groups 1 and 3, and 0.011 between groups 2 and 3. Regarding the glomerular filtration rate, it was 0.46 between groups 1 and 2; 0.001 between groups 1 and 3, and 0.14 between groups 2 and 3.

There were no differences between the groups regarding baseline data on heart rate, blood pressure level, symptom scales, and OAC quality.

### Evolution and Kaplan-Meier curves

During the median follow-up time of 12.0 months [5.0-22.0], bleeding occurred in 76 patients. Current or previous history of systemic embolism occurred in 93 patients. The percentage of patients using OAC was 87.6% in EHRA type 1, 62.2% in type 2, and 56.0% in

**Table 1 – Comparison between groups regarding clinical and laboratory variables and embolism and bleeding scores at the time of entry into the study.**

| Variables | EHRA type 1 | EHRA type 2 | Group 3 | P-value |
|---|---|---|---|---|
| Age (mean ± SD) in years | 50.6 ± 13.0 | 56.8 ± 13.3 | 62.5 ± 14.6 | < 0.0001 |
| Proportion of females | 77.8 | 58.4 | 42.3 | < 0.0001 |
| Permanent AF (%) | 68.1 | 62.2 | 52.5 | 0.004 |
| Basal HR (bpm) Q2 | 80.0 | 78.0 | 76.5 | 0.26 |
| Basal BP (mmHg) Q2 | 114/70 | 113/71 | 120/74 | 0.09/0.36 |
| Average LA diameter (mm) | 55.3 | 52.5 | 48.3 | < 0.0001 |
| LV systolic diameter (mm) Q2 [Q1-Q3] | 32.0 [28-39] | 38 [31-48] | 43 [33-55] | < 0.0001 |
| LVEF Q2 [Q1-Q3] | 0.62 [0.54-0.66] | 0.61 [0.41-0.66] | 0.48 [0.31-0.63] | < 0.0001 |
| OAC usage (%) | 87.6 | 62.3 | 52.2 | < 0.0001 |
| Patients with PM (%) | 3.5 | 5.6 | 18.8 | < 0.0001 |
| $CHA_2DS_2$-VASc | - | 2.3 | 2.9 | < 0.017 |
| GFR (mL/min/1.73 $m^2$) | 96.4 | 88.3 | 76.5 | < 0.0001 |
| $CHA_2DS_2$-VAScRAF | - | 9.9 | 10.1 | 0.85 |
| CCS Symptom Scale | 2.6 | 2.7 | 2.7 | 0.39 |
| EHRA Symptom Scale | 2.7 | 2.7 | 2.80 | 0.73 |
| OAC Quality (%) | 47.5 | 40.9 | 52.7 | 0.08 |
| HAS-BLED Score | 1.4 | 1.6 | 1.7 | 0.06 |
| ATRIA Score | 1.4 | 1.1 | 2.0 | 0.001 |

*SD: standard deviation; AF: atrial fibrillation; HR: heart rate; BP: blood pressure; LA: left atrium; LV: left ventricle; EF: ejection fraction; Q2: median; Q1-Q3: interquartile range; OAC: oral anticoagulant; PM: cardiac pacemaker; GFR: MDRD (Diet Modification in Kidney Disease) glomerular filtration rate; CCS: Canadian Cardiovascular Society; EHRA; Evaluated Heart valves, Rheumatic or Artificial; LVEF: Left Ventricular Ejection Fraction.*

group 3 (< 0.0001). The quality of OAC with INR in the therapeutic range ≥ 60% was 31.8% in EHRA type 2, 22.5% in type 2, and 38.9% in group 3 (p = 0.14).

The outcome was cardiac death in 45 patients, totaling 62 deaths from all causes. A higher cardiac mortality rate was observed in patients with LVEF < 0.40 (24.4%) compared to patients with preserved LVEF (4.7%) and intermediate LVEF (9.5%), with p-value < 0.0001 by the Log-rank test.

No difference was observed between the groups regarding the occurrence of bleeding, embolism, cardiac death, or combined events. There was higher mortality from all causes in group 3 (Table 2). Kaplan-Meier survival curves based on events are shown in Figures 1 to 5. Also, Table 3 shows the accumulated survival percentages of the three groups in relation to the occurrence of general death. The estimated mean survival time for the entire population was 49.9 ± 2.5 months, 95% confidence interval of 45.0 to 54.8 months. There was no difference between sexes regarding cardiac death (p = 0.33) in the entire population.

## Discussion

In this current study involving AF patients categorized by EHRA functional types 1, 2, and those without valvular heart disease, several key findings emerged: The type 1 group exhibited younger age and a higher proportion of women. Conversely, group 3 showed greater left ventricular systolic dysfunction and more pronounced renal impairment, resulting in higher ATRIA scores. Despite a higher rate of OAC use in EHRA type 1, the incidence of systemic embolism and bleeding was similar across all groups, unaffected by the type of OAC

**Table 2 – Comparison between groups regarding separate and combined events**

| Variables | EHRA type 1 | EHRA type 2 | Group 3 | P-value |
|---|---|---|---|---|
| Bleeding (%) | 21.2 | 24.5 | 15.3 | 0.44 |
| Systemic TE (%) | 24.7 | 15.0 | 22.3 | 0.61 |
| Cardiac death (%) | 7.1 | 7.5 | 12.9 | 0.13 |
| Total death (%) | 8.8 | 9.4 | 18.4 | 0.02 |
| Combined events (%) | 30.1 | 41.5 | 44.7 | 0.14 |

*P-value by log-rank test (Mantel-Cox); TE: prior thromboembolism and during follow-up; EHRA: Evaluated Heart valves, Rheumatic or Artificial.*

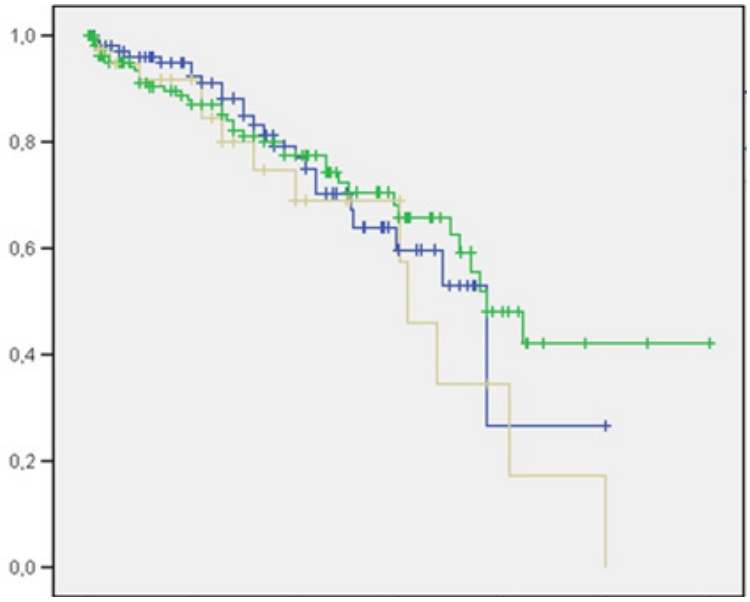


**Figure 1 – Kaplan-Meier survival curve regarding the occurrence of clinically relevant and non-relevant bleeding resulting from OAC between EHRA groups type 1 (blue curve), type 2 (gray), and group 3 (green). Horizontal axis: time in months; vertical axis: probability of survival.**

used, including warfarin. Group 3 showed a higher overall mortality rate, particularly among those with reduced LVEF.

The characteristics observed in the EHRA type 1 group align with existing literature. MS, primarily of rheumatic origin, predominantly affects females (66-68%) around the end of the third decade of life. When AF develops in these patients, it tends to correlate with advancing age, averaging 41.5 years.[18-20] Furthermore, LA dilation due to elevated pressure, chronic inflammation, and fibrosis is commonly observed in patients with both clinical conditions.[19]

When comparing the studies that included the categorization groups with this study, the proportion of EHRA type 1 patients was higher in this study (31.6%), being 4%,[7] 8.4%[11] or 10%,[8] in studies with EHRA type 1 and 2 patients. Conversely, EHRA type 1 patients in this study were characterized by older age, a higher proportion of women, and more frequent permanent AF with OAC use,[7,11] mirroring findings from similar studies. The prevalence of left ventricular dysfunction in group 3 in our study corresponds with findings reported by Bisson et al.[7]

OAC underutilization is still a global challenge. Among 11,056 eligible patients without valvular heart

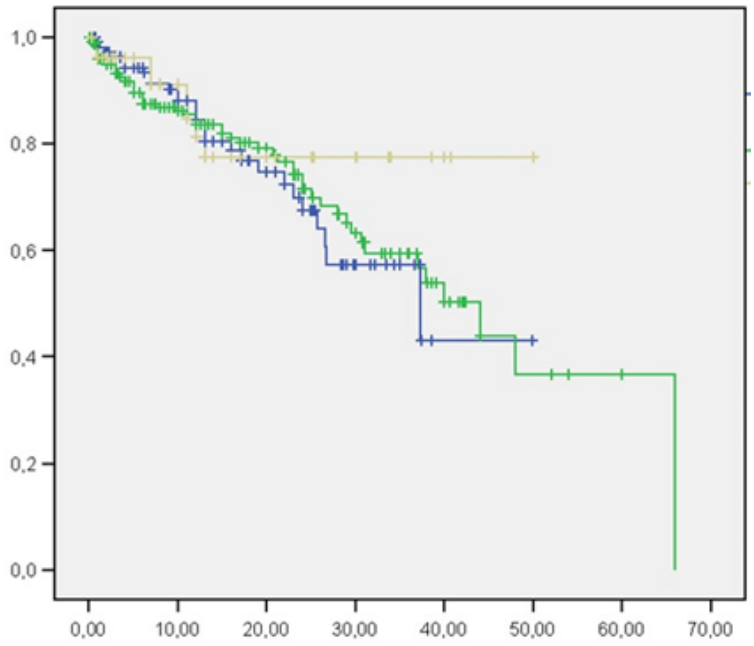


**Figure 2 – Kaplan-Meier survival curve regarding the occurrence of systemic thromboembolism between EHRA groups type 1 (blue curve), type 2 (gray), and group 3 (green). Horizontal axis: time in months; vertical axis: probability of survival.**

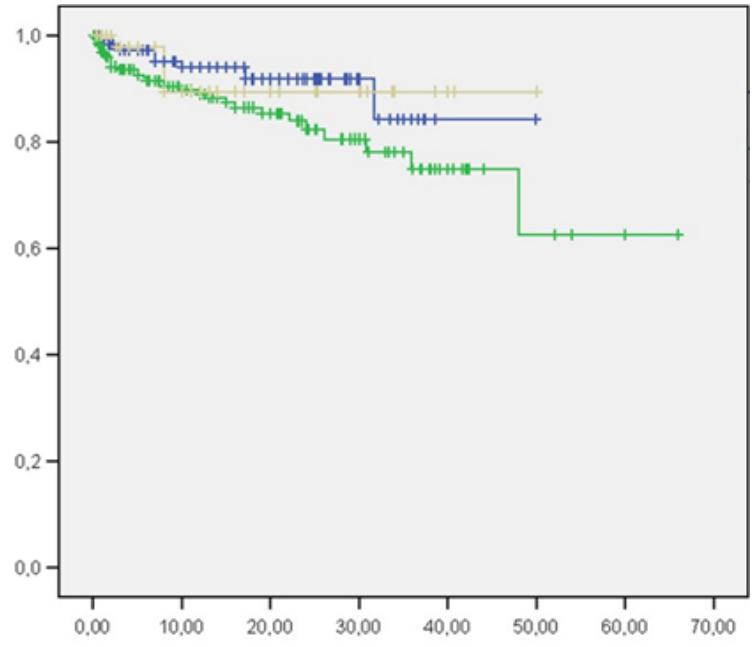


**Figure 3 – Kaplan-Meier survival curve for the occurrence of cardiac death between EHRA groups type 1 (blue curve), type 2 (gray), and group 3 (green). Horizontal axis: time in months; vertical axis: probability of survival.**

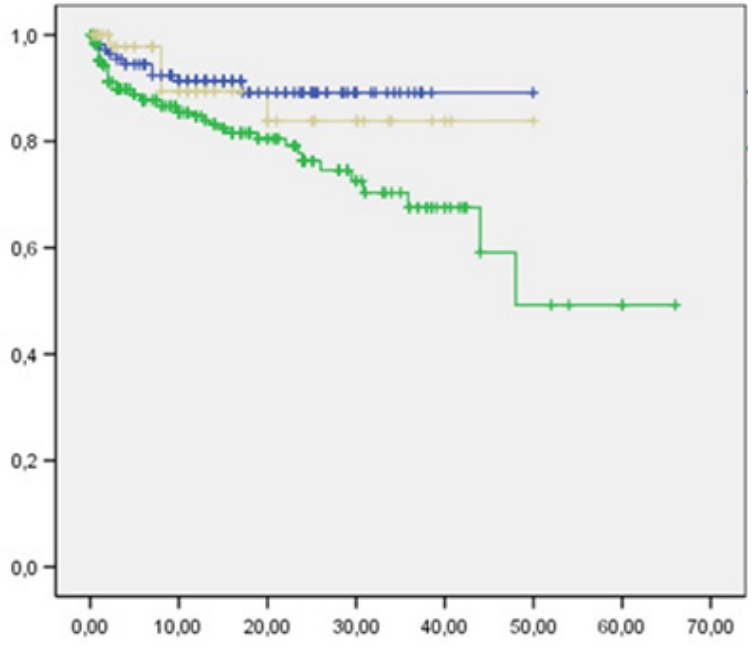


**Figure 4 – Kaplan-Meier curve for total mortality between EHRA groups type 1 (blue curve), type 2 (gray), and group 3 (green). See Table 3. Horizontal axis: time in months; vertical axis: probability of survival.**

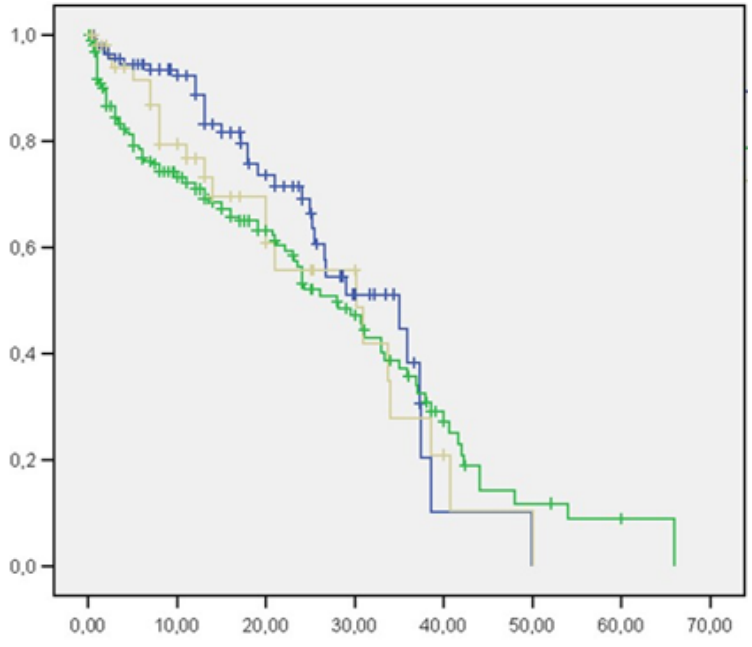


**Figure 5 – Kaplan-Meier survival curve for the occurrence of combined events between EHRA groups type 1 (blue curve), type 2 (gray), and group 3 (green). Horizontal axis: time in months; vertical axis: probability of survival.**

**Table 3 – Cumulative percentage of total mortality-free survival between the groups EHRA type 1, type 2, and group 3.**

| Groups/ time (months) | 6 | 12 | 24 | 30 |
|---|---|---|---|---|
| Cumulative survival percentage (%); EHRA type 1 | 97.3 | 94.5 | 89.1 | 89.1 |
| Cumulative survival percentage (%); EHRA type 2 | 97.8 | 89.4 | 89.4 | 83.8 |
| Cumulative survival percentage (%) group 3 | 87.8 | 84.7 | 76.3 | 72.5 |

*EHRA: Evaluated Heart valves, Rheumatic or Artificial*

disease, 65.5% were receiving OAC, predominantly direct anticoagulants such as rivaroxaban.[19] In emergency settings, only 53.5% of AF patients were initiated on OAC.[21] Among AF patients with rheumatic heart disease, OAC use ranged from 70% to 77%, yet only 37% had received INR follow-up in the past six months, with 22.2% achieving therapeutic range.[22]

Nationally, the quality of OAC management parallels that of developed countries. Recent retrospective studies reported INR within the therapeutic range in 52.2% of AF patients without valvular heart disease in a tertiary hospital setting and 31% among those treated within the private healthcare network. These data are in agreement with the study in question.[23,24]

The prospective RECALL study, a Brazilian AF registry study, recently published,[25] included 4,544 patients with AF from 89 centers (46% female), with an average age of 70 years. This study demonstrated that among those (62.6%) using warfarin, only 42.5% had a baseline INR value within the therapeutic range. Fortunately, in the 12-month follow-up, this proportion increased, reaching 59.1%. However, the use of OAC increased from 88% to 87.1%. These findings, which exhibit higher rates compared to those observed in the present study, likely reflect the impact of that particular research project on adherence to guidelines for managing socially significant AF.

The association between AF and thromboembolic events, as well as bleeding complications associated with OAC, are well-established risks that guide clinical guidelines, supported by scoring systems for OAC usage and management. In recent cohort studies, the rates of stroke and major bleeding, including intracerebral hemorrhage, among AF patients were 0.9% and 6.1% (with warfarin) over a 1.5-year follow-up period,[26] and 9.7% and 5.8% (with any OAC) over 15 months,[27] respectively. These rates were lower than those observed in the present study, potentially due to our inclusion of systemic thromboembolism history (whether cerebral or not) and bleeding (major or minor). However, stroke rates reported by Paciaroni et al.[27] ranged from 8.4% to 17.2% with any OAC, highlighting the high risk of recurrence in AF patients with previous stroke, irrespective of OAC continuity during follow-up. In our study, although not statistically significant, the EHRA type 1 group showed the highest rate of systemic embolism history (prior or during follow-up), accounting for 31.6% of the sample, contributing to the observed higher rate compared to referenced studies. Consistent with studies comparing the three EHRA groups,[7,11] similar to ours, there was no significant difference in adjusted bleeding rates among them.

Regarding AF-related mortality, there is a regional variation, as described in the introduction of this article, of 17%/year in South America, but increased when associated with heart failure, reaching 30%.[2] None of the studies[7-11] using the EHRA categorization assessed this endpoint during follow-up. In the RECALL[25] study, annual mortality was 5.74%. In our study, cardiac mortality was similar between the groups, with a difference in total mortality, higher in group 3 (18.4% in 12 months), in which there was more systolic ventricular dysfunction, that is, lower than that reported in the recent literature.[2] On the other hand, despite the bidirectional relationship between AF and heart failure, with a higher prevalence in patients with reduced LVEF and the influence of this fraction on total mortality,[28] an increased risk of death was observed in AF patients, even with preserved LVEF when compared to those without AF, but with greater mortality for everyone as LVEF decreases, reaching 45% in 3.3 years.[29]

## Limitations

The main limitation was the population size, with a different distribution in terms of group size. There was no assessment of inappropriate use of oral anticoagulants,

including data on dosing and adherence, and other approaches such as ablation, carotid filter placement, and percutaneous occlusion of the LA appendage were not evaluated. Dunn's test was not performed for multiple comparisons related to the Kruskal-Wallis test.

## Conclusion

Despite the higher proportion of OAC in the EHRA type 1 group, there was no difference between the groups in the rates of bleeding, embolism, or combined events. A higher rate of cardiac mortality was observed in patients with reduced LVEF. Total mortality was higher in group 3, with older age, and greater systolic and renal dysfunction.

## Author Contributions

Conception and design of the research, statistical analysis and critical revision of the manuscript for intellectual content: Silva RMFL; acquisition of data, analysis and interpretation of the data: Silva RMFL, Diniz LT, Gomes LSS, Borges LE; writing of the manuscript: Silva RMFL, Borges LE; medical record review: Diniz LT, Gomes LSS.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the UFMG under the protocol number 84057618.8.0000.5149. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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