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Inaugural Atrial Fibrillation in the Emergency Department in adults under 65 years of age

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DEDICATÓRIA

Em especial, à minha mãe, irmão e namorado que são os meus pilares em tudo na vida, sendo o motivo da minha força para nunca desistir. Às minhas amigas, de infância e da faculdade, que sempre estiveram lá quando precisei de apoio nos momentos mais difíceis. E, por último, um especial obrigada à Catarina que me deu um grande auxílio com a sua experiência, sempre com uma enorme generosidade.

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ABSTRACT

Introduction and objectives: Atrial Fibrillation prevalence is growing, namely in younger ages. In these, few studies exist related to atrial fibrillation clinical impact and approach. We aimed to study the clinical correlates, therapeutic strategies and prognostic predictors of patients with inaugural atrial fibrillation under 65 years old.

Methods: A retrospective analysis based on clinical process data of patients discharged from emergency department with atrial fibrillation diagnosis was performed. Only patients with <65 years and previously unknown atrial fibrillation were included to further analyze their baseline characteristics, in-hospital management and cardiovascular outcomes.

Results: The study population consisted of 120 patients, 42.5% female and mean age of 56±7 years old. Most patients (58.3%) had >56 years old and the minority (10%) had <45 years. Hypertension (54.2%), dyslipidemia (50.0%) and overweight/obesity (72.5%) were the most prevalent comorbidities. 69.2% were stratified as moderate-high CHA₂DS₂-VASc risk. 59.2% presented on emergency department with atrial fibrillation for \geq 48h and in 62.5% a frequency control strategy was chosen. Oral anticoagulation was prescribed in 75.0% of patients with formal indication. No reasons were appointed for not prescribing in the remainder. 81.7% of patients with transthoracic echocardiography evaluation had some structural cardiac abnormality. Heart failure was the most prevalent complication on follow-up (37.5%) and significantly associated with higher CHA₂DS₂-VASc score (3.0±1.4, p=0.01), alcohol consumption (25.0%, p=0.01) and smoking (55.6%, p=0.03).

Conclusions: This study shows that the age and comorbidities remain important to AF development in younger ages. As expected heart failure was the most relevant atrial fibrillation complication. Adherence to guidelines

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recommendations, primarily in thromboembolic prevention was sub-optimal but reflects a favorable trend in contemporary clinical practice when compared to similar studies.

Bibliography: PubMed database accessed between September 2018 and May 2019.

Keywords: *Atrial fibrillation, Emergency department, Population characteristics, Follow–up study, Heart failure, Guidelines*

RESUMO

Introdução e objetivos: A prevalência da fibrilação auricular está a aumentar, nomeadamente em idades mais jovens. Poucos estudos existem relativamente ao impacto clínico e abordagem da fibrilação auricular nestes doentes. O nosso objetivo foi estudar as correlações clínicas, abordagens terapêuticas e preditores de prognóstico de doentes com fibrilação auricular inaugural de idade inferior a 65 anos.

Métodos: Foi realizada uma análise retrospetiva baseada em dados do processo clínico de doentes com diagnóstico de fibrilação auricular aquando da alta do episódio de serviço urgência. Apenas doentes com menos de 65 anos e com fibrilação auricular previamente desconhecida foram incluídos para análise posterior das suas características de base, abordagem intra-hospitalar e resultados cardiovasculares.

Resultados: A população de estudo incluiu 120 doentes, 42.5% do sexo feminino e idade média de 56±7 anos. A maioria dos doentes (58.3%) tinha >56 anos e a minoria (10%) tinha <45 anos. Hipertensão (54.2%), dislipidemia (50.0%) e excesso de peso/obesidade (72.5%) foram as comorbilidades mais prevalentes. 69.2% pertenciam ao grupo de risco moderado a alto de CHA₂DS₂-VASc. 59.2% apresentaram-se no serviço de urgência com FA de duração \geq 48h e para 62.5% foi selecionada uma estratégia de controlo de frequência cardíaca. Foi prescrita anticoagulação oral em 75.0% dos doentes com indicação formal. Não estavam descritos motivos para a não prescrição nos restantes. 81.7% dos doentes com avaliação ecocardiográfica tinham alguma alteração cardíaca estrutural. A insuficiência cardíaca foi a complicação mais prevalente durante o follow-up (37.5%) e o seu desenvolvimento relacionou-se significativamente com um score de CHA₂DS₂-VASc mais elevado (3.0±1.4, p=0.01), consumo de álcool (25.0%, p=0.01) e tabagismo (55.6%, p=0.03).

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Conclusões: Este estudo demonstra que a idade e as comorbilidades permanecem importantes para o desenvolvimento de FA em idades mais jovens. Como esperado, a IC foi a complicação mais relevante. Apesar de ainda existir falhas na adesão às recomendações das *guidelines*, principalmente em termos de prevenção tromboembólica, revelou-se uma tendência favorável na prática clínica contemporânea, quando comparada com estudos prévios similares.

Bibliografia: Acesso à base de dados da PubMed entre Setembro de 2018 e Maio de 2019.

Palavras-chave: Fibrilação auricular, Serviço de urgência, Características da população, Estudo de Follow-up, Insuficiência cardíaca, Guidelines

ABBREVIATIONS LIST

AIC arrhythmia-induced cardiomyopathy
AF atrial fibrillation
CAD coronary artery disease
CHUP Centro Hospitalar Universitário do Porto
CV cardioversion
ED emergency department
HF heart failure
HTN hypertension
ICD-10 International Statistical Classification of Diseases and Related Health Problems
LA left atria
LV left ventricle
LVEF left ventricle ejection fraction
MI mitral insufficiency
OAC oral anticoagulation
RV right ventricle
SD standard deviation
SPSS Statistical Package for the Social Sciences
TIA transient ischemic attack
TTE transthoracic echocardiography
yo years old

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INTRODUCTION

Atrial Fibrillation (AF) is the most frequent sustained arrhythmia in clinical practice, estimated to affect up to 25% of the population above 40 years old (yo)¹, reaching up to 17% of Europeans over 80 yo.²

AF prevalence increases with age and with comorbidities such as hypertension (HTN), heart failure (HF), coronary artery disease (CAD), valvular heart disease, obesity, diabetes and chronic kidney disease.^{2–5} In Portugal data are scarce. FAMA study determined an overall AF prevalence of 2.5% in patients older than 40 yo.⁶ AF prevalence will likely increase in the next years, due to the ageing population, increase of comorbidities and improved methods of detection. ^{2–5,7}

Furthermore, recent studies show a growing prevalence in younger groups, with a simultaneous increase in hospitalizations, thromboembolic risk score and stroke. This is thought to be related with lifestyle changes in the last decades, associated with increased obesity and HTN.^{8,9}

These younger populations have interesting particularities, such as their specific pathophysiological mechanisms, risk factors, clinical evolution and management strategies. However, further investigations are needed to correctly characterize these particularities.^{5,8,10-12}

Whilst AF is more common when comorbidities coexist^{8-11,13}, it may also occur in individuals without any other evident disease, known as 'lone AF', which is more common in younger ages. Conversely it can also occur as the first manifestation of a clinically silent cardiac disease. ^{5,8,10-12}

AF remains one of the main causes of cardiovascular morbidity, namely stroke, HF and sudden death.^{3,14,15} The association between AF and HF is well established. However, their temporal connection is harder to define not only because do they share common risk factors but also each one can predispose to the other. This may have a marked adverse influence on prognosis.^{16,17} Arrhythmia-induced cardiomyopathy (AIC) can occur in patients with persistent rapid AF, that can lead to severe HF, typically partial or completely reversed when arrhythmia control is achieved.^{12,18,19}

Therapeutic management focus on symptoms relief, through rhythm or frequency control, and on complications prevention.^{8,11} Oral anticoagulant (OAC) therapy is highly effective in preventing thromboembolic events and improves overall outcomes.^{4,8,20,21} Cowan J. et al²², in a 10 year study, showed that AFrelated stroke rates declined and it was significantly associated with the increase of OAC prescription. Thromboembolic risk stratification of non-valvular AF relies on CHA₂DS₂-VASc score.^{4,11} According to this score, in younger ages (<65 yo) without any other comorbidity (score of 0 in men and 1 in women) the annual thromboembolic risk is very low, so OAC is not recommended. On the other hand, men with score \geq 2 and women with score \geq 3, OAC is strongly recommended.^{8,11,23}

Rhythm control offers no clear advantage when compared to rate control in major adverse cardiovascular events in the overall AF population.^{8,23-25} Nevertheless, studies demonstrated that rhythm control is beneficial in younger patients with or without symptoms.^{8,11} One possible reason that supports this is the higher probability of sinus rhythm reversion and maintenance in early stages, preventing AF progression and improving prognosis.⁸

AFFIRM study²⁴ evidenced that despite sinus rhythm maintenance has survival benefits, currently antiarrhythmic drugs have the opposite effect. These results led to the emergence of new rhythm control strategies in the last few years, like AF ablation, which has gained considerable weight in long term management of some patients, particularly in young patients with 'lone AF'.^{8,11,15,26,27}

<u>Objectives</u>:

We aimed to study the clinical correlates, therapeutic strategies and prognostic predictors of patients with inaugural AF under 65 yo.

MATERIAL AND METHODS

An observational longitudinal retrospective study was performed including all consecutive patients discharged from the ED of *Centro Hospitalar Universitário do Porto* (CHUP), between June 2015 and June 2017, with AF or AF/Atrial Flutter as final diagnosis, according with ICD–10 coding. After reviewing the ED clinical records and electrocardiograms, only patients under 65 yo, presenting with an inaugural episode of AF, were included for further analysis. We studied demographic and clinical variables, assessed the ED and ambulatory management of AF regarding to initial approach, selection of pharmacological therapy and anticoagulation strategies. Echocardiographic assessment either performed in the ED or shortly after was also included for analysis. Lastly, we looked to major adverse cardiovascular events during follow–up and focused more specifically in HF. The collected data was anonymized by assigning a number to each patient and its confidentiality was guaranteed by storing and password protecting it. Since the subjects of the study were not submitted to any intervention, there was no need to obtain informed consent, as judged by the Ethic Committee.

The statistical analysis was performed using SPSS version 25. The descriptive analysis of numerical variables included calculation of the minimum, maximum, mean, median and standard deviation (SD). The categorical variables were evaluated and expressed as a percentage rounded to one decimal point. Bivariate analysis of pairs of categorical variables was performed using contingency tables and the chi-square test. Numerical variables were compared using t tests for independent samples. Logistic regression models were used to assess to predict outcomes.

RESULTS

During the study period, 918 patients were discharged from ED with a diagnosis of AF or AF/atrial flutter, and 207 (22.5%) were under 65 yo. 120 patients (58.0%) met the study inclusion criteria and were further analyzed.

The average age was 56 ± 7 yo (min=37, max=64; median 58) and the age group distribution is shown on Figure 1. 42.5% (51) were female. Mean CHA₂DS₂– VASc score was 1.5 ± 1.1 points (1.0 ± 0.9 in men and 2.1 ± 1.2 in women) and CHA₂DS₂–VASc score distribution by gender is shown on Figure 2. According to total score, patients were included in different thromboembolic risk groups: men who scored 0 and women who scored 1 were considered as low risk; men with 1 point and women with 2 as moderate risk; and men with ≥ 2 and women with ≥ 3 as high risk. HTN (54.2%), dyslipidemia (50.0%), overweight/obesity (72.5%) and smoking (37.5%) were the most frequent comorbidities. Of the 45 smoking patients, 9 were women and 36 were men. The results related with other analysed comorbidities are shown on Figure 3.

Regarding to ED presentation and management (Table I), 59.2% had AF for \geq 48h. AF related symptoms – palpitations, chest pain, dyspnea, fatigue, or lightheadedness – were present in 80.0% of patients. 4.2% presented hemodynamically unstable and had to be urgently cardioverted.

In 62.5% of patients a frequency control strategy was chosen. In these, 20.0% spontaneously reverted to sinus rhythm during ED stay. Rhythm control was chosen in 37.5% and was successful in 88.9% of them. Patients who needed frequency control intervention on top of rhythm therapy were assigned to the rhythm control group. Of the patients with AF for \geq 48h and not previously anticoagulated (total of 63 patients), 4.8% (3 patients) were subjected to a rhythm control strategy in ED. None of these corresponded to those who were considered hemodynamically unstable. OAC was used at discharge in 67.5% of all studied

patients and its distribution by gender and CHA₂DS₂–VASc score are shown on figure 4. 71.4% of men and 78.6% of women with high thromboembolic risk received OAC (75.0% of total patients included in this risk group). The reasons for OAC not being proposed in the other patients of this group were not reported. Furthermore, 38.9% of men and 47.4% of women with low thromboembolic risk were anticoagulated (43.2% of total patients included in this risk group). In one of these men, OAC was prescribed after an electrical cardioversion (CV) approach during ED with the intention to keep it for 4 weeks. However, his follow–up was lost. In two of these women, OAC was prescribed with the intent to electrically cardiovert them on a posterior evaluation. The reasons to anticoagulate the remaining low risk patients, weren't made explicit. NOACs were preferred in 81.5% of these patients. Regarding the approach at discharge, 35.0% of patients remained under rhythm control strategy (16.7% without antiarrhythmics but with intent to electrical CV) and 65.0% under frequency control. After discharge, 77.5% were referred to cardiology consultation for follow–up.

A transthoracic echocardiography (TTE) was performed in 81.7% of the patients either in the ED (35.7%) or in the subsequent weeks (83.7%). TTE findings are shown on Table II. 81.7% of the patients had at least one structural alteration on TTE. Average indexed atrial volume was 46.9 ± 13.9 mL/m² and 39.8% had moderate to severe dilatation of the left atria (LA). 53% had mitral insufficiency (MI) and 10.2% of these had a moderate to severe degree. Qualitative assessment of the left ventricle (LV) was performed in all patients with 6.2% showing moderate to severe LV enlargement and 23.4% presenting systolic dysfunction. Right ventricle (RV) function was normal in 93.9% of patients and only 1 had moderate dilation. 62.2% had other structural disease, such as valvular heart disease or congenital disease. In 32 (33.3%) patients, the NT-pro-BNP value was

determined (96.9% during follow-up) and 29 (90.6%) having had a value above 125 pg/mL.

Median follow-up time was of 24 ± 10 months and 20% of patients were lost.

During follow-up, 22.9% underwent elective electrical CV, however 59.1% of these had AF recurrence. 6.3% underwent AF ablation, with 33.3% of recurrence.

Adverse events are described in Table III. 29.2% returned to ED due to AF related symptoms. 11.3% (7 patients) of patients on OAC had hemorrhagic complications. All of these were minor (epistaxis and minor gastrointestinal bleeding), except in one patient who suffered intracranial hemorrhage (subsequently referred to percutaneous LA appendage closure). One patient had a stroke/transient ischemic attack (TIA) under NOAC and 3 died, 1 due to AKI and the rest for reasons that couldn't be elucidated. No other adverse events were reported.

HF was the most frequent complication associated with AF, affecting 37.5% of patients during follow-up. Given the relevance of these results, this subpopulation was further characterized.

Of 36 patients with HF symptoms, 52.7% presented with HF already at the index event and 47.3% developed HF symptoms in follow-up (Figure 5). 41.7% had at least one subsequent hospitalization for decompensated HF (Table III). NT-pro-BNP value was evaluated in 19 of the 36 HF patients and all of them had a value above 125 pg/mL (median NT-pro-BNP: 1,019±12,294 pg/mL). AF patients who developed HF were less likely to be successfully cardioverted in the ED (19.4% vs 43.3% p=0.017) and more likely presented on ED with AF for \geq 48h (83.3% vs 60.0%, p= 0.017). HF group correlated with a higher CHA₂DS₂-VASc score (1.3±0.9 vs 3.0±1.4, p=0.01), excessive alcohol consumption (25.0% vs

6.7%, p=0.011) and smoking (55.6% vs 33.3%, p=0.03). In TTE evaluation, they were more likely to have moderate to severe LA enlargement (72.2% vs 23.2%, p<0.01) with a median indexed atrial volume of 50 ± 14 mL, LV enlargement (38.9% vs 3.6%, p<0.01) and moderate to severe systolic dysfunction (44.4% vs 3.6%, p<0.01) with a mean left ventricle ejection fraction (LVEF) of 30 ± 16 %, more RV dysfunction (16.7% vs 0.0%, p=0.02) and more significant MI (25.0% vs 1.8%, p<0.01).

DISCUSSION

This study describes the "real world" practice of AF approach at a Portuguese tertiary hospital ED, specifically in a subpopulation in which the major determining contributing factor – advanced age – was eliminated and where few studies were conducted.

Age retains its importance as a major risk factor in the younger population, as demonstrated by the higher proportion of patients in each age group (<45, 45-55, 55-65) as age increases, like evidenced in other studies.^{6,13}

Cardiovascular risk factors were frequent in the study population. HTN and dyslipidemia were the most common comorbidities. In addition to these, patients had a high prevalence of obesity and overweight. Similar results have been reported in other Portuguese studies^{4,13,15}, however most of these studies were conducted in the general AF population, meaning a higher average age. Monteiro P. et al¹³ and Dores H. et al⁴, reported an average age of 68.9 and 77.0 yo, respectively, and also a higher burden of comorbidities. These results support the positive association between advanced age and comorbidities. An important exception is the FAMA study⁶, a population based screening study, where the average age was similar to our study (58 yo) in which the prevalence of the mentioned comorbidities was slightly lower (HTN 43%, dyslipidemia 37%, mean body mass index 27.7 kg/m²).⁶ In these younger patients, the relative weight of comorbidities to the development of AF seems to be higher. Furthermore, the high burden of comorbidities was also reflected in an increased thromboembolic risk).

Smoking stood out for being significantly higher in the present study than previously reported, primarily in males (80.0% of the smokers). Accordingly to Ahmad et al²⁸, smoking is associated with an increased AF risk, primarily in the younger groups. Contrarily to the present study, in Framingham Heart Study²⁹ this association was present in females.

The TTE analysis added important information with prognostic impact and increases the relevance of this study, since it is usually missing in other AF studies. More specifically, it provided data on LVEF, an important prognostic marker, valvular disease which is frequently associated with AF, and atrial volume. LA enlargement is an independent risk factor to early development into chronic AF³⁰, so its finding can signal an increased probability of long-standing AF. In the present study, a significant number of patients had structural abnormalities (81.7%). One possible explanation is that the underlying AF mechanism in these patients is not based entirely on a "pure" cardiac rhythm disorder but part of a more complex pathophysiological process, similar to the one already evidenced in older AF populations. These changes in cardiac morphologic substrate and the prevalence of comorbidities may contribute to the low effectiveness of elective electrical CV and ablative techniques observed. In fact, previous studies³¹ have shown that a higher atrial volume and number of comorbidities correlate negatively with the success of ablation.

In the index ED episode, some issues on guidelines recommendations adherence were noticed. Most patients (59.2%) had AF for \geq 48h. Three of these patients, not previously anticoagulated, were submitted to rhythm control strategy. OAC was used in 75.0% of patients with formal indication. In the remainder 25.0% the reasons not using OAC were not clearly stated. Dores H. et al⁴ also demonstrated a low rate of anticoagulation with 51.6% of patients with high thromboembolic risk receiving OAC and so did an older study³² reporting 46.0% of adherence to recommendations. Furthermore, in these studies, the reasons not to anticoagulate were also not fully known. Numerous authors justify these low rate of OAC prescription in high risk patients by the apprehensiveness

of hemorrhagic complications, primarily in the elderly.^{4,33} This extrapolation cannot be made in the present study, given the younger age of the patients included. Nevertheless, there seems to be a positive increase in appropriate OAC use over the years and our study builds up on that evidence reporting a 75.0% of patients adequately anticoagulated. This tendency was also shown in Cowan J. et al²², with an increase of OAC prescription of 48.0% to 78.6% between 2006 and 2016.

Another aspect that should be highlighted is that a large percentage (83.0%) of patients in the moderate risk group was anticoagulated. Recommendations concerning OAC benefit in these patients are still a matter of debate.^{23,34} For example, while Hung et al³⁴ support an OAC benefit in young patients with only one additional risk factor (despite of gender), Coppens M. et al³⁵ concluded that stroke risk in this patients has no sufficiently relevance to support OAC therapy. Thus, according to current recommendations OAC prescription in this group is acceptable and an individualized patient-based decision is proposed.²³

Data from all observational studies suggests that, despite great evolution, there is still need of improvement in thromboembolic prevention. Lastly, further studies may help us define the real benefit of OAC use in the lower risk groups.

HF was the most important complication in the studied population, with 36.5% of patients having symptoms. In another Portuguese study⁴, HF had a similar prevalence (36.6%), but the average age of the studied population was higher than in the present study. In The Framingham Heart Study¹⁶, 42% had HF at some point during their lifetime. This study was capable of examining temporal relationship between AF and HF, observing that AF preceded HF about as often as HF preceded AF. This was not verified in our study, in which the majority developed HF during follow-up. This may be explained by the great

influence of AF in cardiac substrate, which can lead to HF over time. The development of HF correlated positively with excessive alcohol consumption and smoking. The well-known direct toxic damage of alcohol in cardiac tissue and the association between smoking and cardiovascular disease probably explain these associations.³⁶ Patients with HF had more structural abnormalities on TTE compared to those without it. LV dysfunction was present in 23.4% of patients with echocardiographic evaluation with a more severe expression in HF patients (44.4% vs 3.6%, p < 0.01 moderate to severe impairment). Although some of these cases might be attributable to AIC, this conclusion cannot be taken since data on echocardiographic re-evaluation are lacking. Also, of notice, is the higher proportion of moderate to severe MI in the HF sub-group (25.0% vs 1.8%, p<0.01) reflecting the link between both conditions. We can speculate that MI in this group was mostly functional given the higher LV enlargement found (38.9% vs 3.6%, p < 0.01). These structural abnormalities reflect an ongoing remodeling process and may relate to lower cardioversion success and maintenance of sinus rhythm.

There weren't any differences in mortality or adverse events (such as stroke), but this might be explained by short follow-up time and small sample size. Like in other studies of young patients¹⁰, the incidence of stroke or some other thromboembolic events was low during the follow-up of the overall population.

Study limitations:

There are study limitations that should be acknowledged. Its retrospective nature and the fact that it was based on medical records meant that some data could not be completed for all patients. Another limiting factor relates to using CHA₂DS₂-VASc score to assess thromboembolic risk since this score was studied

in older populations^{37,38} and data on stroke and thromboembolism risk factors in young patients are scarce.³⁹ Second, the small sample size and the loss of 20% of patients to follow-up posed difficulties with data analysis and validation. Moreover, the study does not represent the totality of new-onset AF on ED, since some cases of other severe AF presentations might have been coded with HF or stroke. The short follow-up time hampered the study power to assess prognosis of the patients who developed HF.

CONCLUSIONS

In our real world study, increasing age and number of comorbidities were associated with AF. The high percentage of echocardiographic abnormalities and of HF symptoms means that a close monitoring of patients at risk is warranted to prevent late presentations. We found a higher rate of adequately anticoagulated patients than previously reported signaling a positive evolution in thromboembolic protection. Further studies focusing on long-term outcomes are necessary in this age group, to better define appropriate management strategies.

APPENDIX

<u>Tables</u>

ED presentation % (n° of patients) ∠48h 40.8 (49) ≥48h or unknown 59.2 (71) Ventricular Response Fast Fast 83.3 (100) Slow 1.7 (2) Normal 15.0 (18) Symptomatic 80.0 (96) HF symptoms 17.5 (21) De novo HF 66.7 (14) HF decompensation 33.3 (7) Hemodynamic instability 4.2 (5) ED management % (n° of patients) Rhythm control 37.5 (45) Pharmacological strategy 77.8 (35) Electrical CV 22.2 (10) Frequency control 62.5 (75) HBPM 52.5 (63) OAC 67.5 (81) NOAC 81.5 (66) VKA 18.5 (15) Rhythm control 35.0 (42) Pharmacological strategy 83.3 (35) Electrice electrical CV 16.7 (7) Frequency control 65.0 (78) Pharmacological strategy 7.5 (94) Elective elect	Table / ED 1 st AF episode ch	naracterization (n=120)
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HF decompensation33.3 (7)Hemodynamic instability4.2 (5)ED management% (n° of patients)Rhythm control37.5 (45)Pharmacological strategy77.8 (35)Electrical CV22.2 (10)Frequency control62.5 (75)HBPM52.5 (63)OAC67.5 (81)NOAC81.5 (66)VKA18.5 (15)Rhythm control35.0 (42)Pharmacological strategy83.3 (35)Elective electrical CV16.7 (7)Frequency control65.0 (78)Orientation77.5 (94)Cardiology77.5 (94)Family doctor15.0 (18)	HF symptoms	17.5 (21)
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Frequency control 62.5 (75) HBPM 52.5 (63) ED Discharge % (n° of patients) OAC 67.5 (81) NOAC 81.5 (66) VKA 18.5 (15) Rhythm control 35.0 (42) Pharmacological strategy 83.3 (35) Elective electrical CV 16.7 (7) Frequency control 65.0 (78) Orientation 77.5 (94) Family doctor 15.0 (18)	Pharmacological strategy	77.8 (35)
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Pharmacological strategy\$3.3 (35)Elective electrical CV16.7 (7)Frequency control65.0 (78)OrientationCardiologyFamily doctor15.0 (18)OthereCardiology	VKA	18.5 (15)
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Frequency control 65.0 (78) Orientation 77.5 (94) Family doctor 15.0 (18)	Pharmacological strategy	83.3 (35)
Orientation Cardiology Family doctor 15.0 (18)	Elective electrical CV	16.7 (7)
Cardiology 77.5 (94) Family doctor 15.0 (18)	Frequency control	65.0 (78)
Family doctor 15.0 (18)	Orientation	
Others	Cardiology	77.5 (94)
Others	Family doctor	
	Others	

AF: atrial fibrillation; CV: cardioversion; ED: emergency department; HF: heart failure; NOAC: non-vitamin K antagonist oral anticoagulants; OAC: oral anticoagulation; VKA: vitamin K antagonists

Cardiac structure alteration LA enlargement	% (n° of patients)
-	
LA indexed volume	$46.9 \pm 13.9 \text{ mL}/\text{m}^2$
Moderate to severe	39.8 (39)
enlargement	59.0 (59)
RA enlargement	
Moderate to severe	5.1 (5)
LV enlargement	
Moderate to severe	6.2 (6)
RV enlargement	
Moderate to severe	1.0 (1)
LV function	
Normal	76.5 (76)
Slight impairment	5.1(5)
Moderate impairment	7.1(7)
Severe impairment	11.2 (11)
RV function	
Normal	93.9 (92)
Impaired	6.1(6)

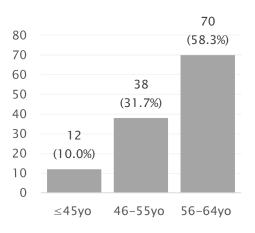
LA: left atria; LV: left ventricle; MI: mitral insufficiency; RA: right atria; RV: right ventricle; TTE: transthoracic echocardiography

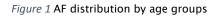
Table III Outcomes during	
Overal outcomes	% (n° of patients)
New ED recurrences for AF	29.2 (28)
Elective electric CV	22.9 (22)
Average CV's number (n°,±SD)	1.3 ± 0.6
Recurrence	59.1 (13)
Mean days until recurrence	137±213
(days,±SD)	137 ± 213
AF ablation	6.3 (6)
Recurrence	33.3 (2)
Long-term OAC	64.6 (62)
Hemorrhagic complications	11.3 (7)
Minor	85.7 (6)
Major	14.3 (1)
Adequate HR control	94.8 (91)
Chronic medication	
Chronic medication Diuretic	39.6 (38)
	39.6 (38) 52.6 (20)
Diuretic	
Diuretic After ED	52.6 (20)
Diuretic After ED Dose increase	52.6 (20) 44.7 (17)
Diuretic After ED Dose increase Suspension	52.6 (20) 44.7 (17) 7.9 (3)
Diuretic After ED Dose increase Suspension ACE-I	52.6 (20) 44.7 (17) 7.9 (3) 54.2 (52)
Diuretic After ED Dose increase Suspension ACE-I B-blocker	52.6 (20) 44.7 (17) 7.9 (3) 54.2 (52) 85.4 (82)
Diuretic After ED Dose increase Suspension ACE-I B-blocker Antiarrhythmic	52.6 (20) 44.7 (17) 7.9 (3) 54.2 (52) 85.4 (82) 47.9 (42)
Diuretic After ED Dose increase Suspension ACE-I B-blocker Antiarrhythmic Cardiovascular outcomes	52.6 (20) 44.7 (17) 7.9 (3) 54.2 (52) 85.4 (82) 47.9 (42) % (n° of patients)
Diuretic After ED Dose increase Suspension ACE-I B-blocker Antiarrhythmic Cardiovascular outcomes HF	52.6 (20) 44.7 (17) 7.9 (3) 54.2 (52) 85.4 (82) 47.9 (42) % (n° of patients) 37.5 (36)
Diuretic After ED Dose increase Suspension ACE-I B-blocker Antiarrhythmic Cardiovascular outcomes HF Hospitalizations	52.6 (20) 44.7 (17) 7.9 (3) 54.2 (52) 85.4 (82) 47.9 (42) % (n° of patients) 37.5 (36) 41.7 (15)

Table III Outcomes during follow-up (n=96)

ACE-I: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; CV: cardioversion; ED: emergency department; HF: heart failure; HR: heart rate; OAC: oral anticoagulation; TIA: transient ischemic attack

<u>Figures</u>





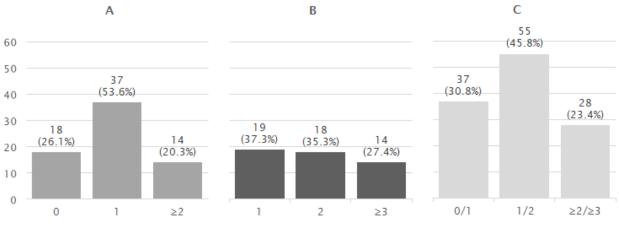


Figure 2 CHA₂DS₂-VASc score distribution by gender. A: male gender; B: female gender; C: total sample.

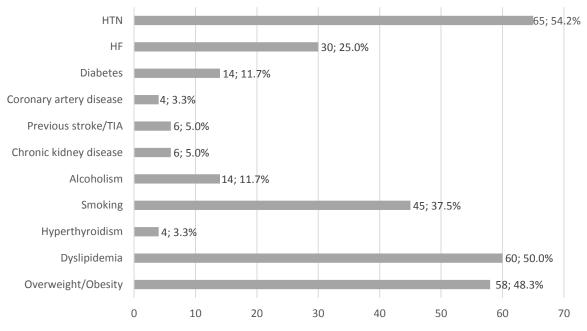


Figure 3 Comorbidities prevalence. HF: heart failure; HTN: hypertension; TIA: transient ischemic attack.

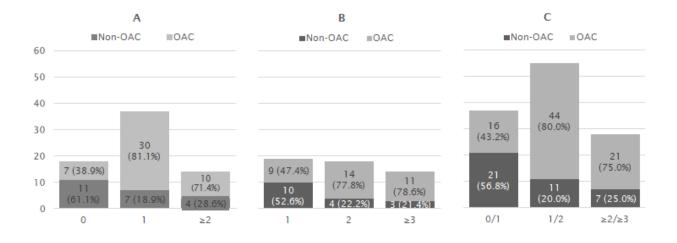
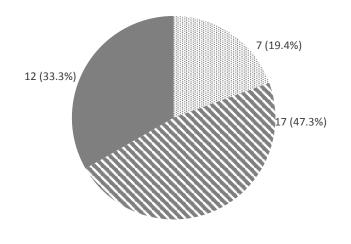


Figure 4 OAC distribution by gender and CHA₂DS₂-VASc score at ED discharge. A: male gender; B: female gender; C: total sample.



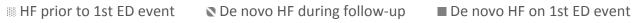


Figure 5 Type of HF presentation on patients with HF on follow-up.

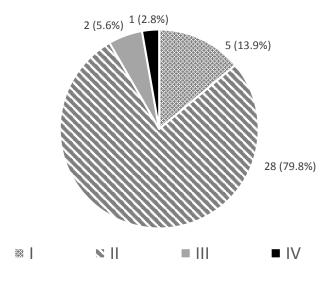


Figure 6 NYHA class among HF patients at presentation.

REFERENCES

- 1. Chugh S, Havmoeller R, Narayanan K, et al. Worldwide Epidemiology of Atrial Fibrillation. *Circulation*. 2014;129(8):837–847.
- 2. Zoni-Berisso M, Lercari F, Carazza T. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol.* 2014;6(1):213.
- Gouveia M, Costa J, Alarcão J, et al. Carga e custo da fibrilhação auricular em Portugal. *Rev Port Cardiol*. 2015;34(1):1-11.
- 4. Dores H, Cardiga R, Ferreira R, et al. Fibrilhação auricular e risco tromboembólico : Que aderência às recomendações na prática clínica? *Rev Port Cardiol*. 2011;30(02):171–180.
- Nattel S. New ideas about atrial fibrillation 50 years on. Nat Int J Sci. 2002;415:219-226. https://www.ncbi.nlm.nih.gov/pubmed/11805846.
- 6. Bonhorst D, Mendes M, Abragão P, et al. Prevalência de fibrilhação auricular na população portuguesa com 40 ou mais anos. Estudo FAMA. *Rev Port Cardiol.* 2010;29(03):331-350.
- 7. Schnabel R, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386(9989):154–162.
- 8. Wasmer K, Breithardt G, Eckardt L. The young patient with asymptomatic atrial fibrillation: what is the evidence to leave the arrhythmia untreated? *Eur Heart J.* 2014;35(22):1439–1447.
- 9. Deshmukh A, Pothineni N, Patel N, et al. Trends in hospitalizations of young patients with atrial fibrillation: A cause for concern? *Int J Cardiol*. 2016;203:164–165.
- 10. Wutzler A, von Ulmenstein S, Attanasio P, et al. Where There's Smoke, There's Fire? Significance of Atrial Fibrillation in Young Patients. *Clin Cardiol.* 2016;39(4):229–233.
- 11. Sankaranarayanan R, Kirkwood G, Dibb K, et al. Comparison of Atrial Fibrillation in the Young versus That in the Elderly: A Review. *Cardiol Res Pract.* 2013;2013(1):1–16.
- 12. Chugh S, Blackshear J, Shen W-K, et al. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol.* 2001;37(2):371–378.
- Monteiro P. Estudo Safira: reflexões sobre a prevalência e os padrões de tratamento de fibrilhação auricular e risco cardiovascular em 7500 indivíduos com 65 ou mais anos. *Rev Port Cardiol.* 2018;37(4):307-313.
- 14. Wolf P, Abbott R, Kannel W. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke*. 1991;22(8):983–988.
 http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L21264953.
- 15. Primo J, Gonçalves H, Macedo A, et al. Prevalência da fibrilhação auricular paroxística numa população avaliada por monitorização contínua de 24 horas. *Rev Port Cardiol.* 2017;36(7-8):535-546.
- 16. Wang T, Larson M, Levy D, et al. Temporal Relations of Atrial Fibrillation and Congestive Heart Failure and Their Joint Influence on Mortality. *Circulation*. 2003;107(23):2920-2925.
- 17. Maisel W, Stevenson L. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol*. 2003;91(6):2–8.
- 18. Gopinathannair R, Etheridge SP, Marchlinski FE, et al. Arrhythmia-Induced Cardiomyopathies. *J Am Coll Cardiol*. 2015;66(15):1714-1728.
- Redfield M, Kay G, Jenkins L, et al. Tachycardia-Related Cardiomyopathy: A Common Cause of Ventricular Dysfunction in Patients With Atrial Fibrillation Referred for Atrioventricular Ablation. *Mayo Clin Proc.* 2000;75(8):790-795.

- 20. Man-Son-Hing M, Nichol G, Lau A, et al. Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls. *Arch Intern Med.* 1999;159(7):677.
- 21. Lip G, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients. *Thromb Haemost*. 2011;106(12):997–1011.
- 22. Cowan J, Wu J, Hall M, et al. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. *Eur Heart J.* 2018;39(32):2975–2983.
- 23. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines For The Management Of Atrial Fibrillation Developedin Collaboration With Eacts. *Russ J Cardiol.* 2017;147(7):7–86.
- 24. Epstein A. Relationships Between Sinus Rhythm, Treatment, and Survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation*. 2004;109(12):1509–1513.
- 25. Hagens V, Ranchor A, Van Sonderen E, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. *J Am Coll Cardiol*. 2004;43(2):241-247.
- 26. Bunch T, May H, Bair T, et al. The Impact of Age on 5-Year Outcomes After Atrial Fibrillation Catheter Ablation. *J Cardiovasc Electrophysiol*. 2016;27(2):141-146.
- 27. Packer D, Mark D, Robb R, et al. Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial: Study Rationale and Design. *Am Heart J.* 2018;199:192–199.
- 28. Ahmad M, Mosley C, O'Neal W, et al. Smoking and risk of atrial fibrillation in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Cardiol.* 2018;71(2):113-117.
- 29. Benjamin E, Levy D, Vaziri S, et al. Independent Risk Factors for Atrial Fibrillation in a Population-Based Cohort. *JAMA*. 1994;271(11):840-844.
- Kato T, Yamashita T, Sagara K, et al. Progressive Nature Of Paroxysmal Atrial Fibrillation Observations From A 14-Year Follow-Up Study. In: *Advances in Electrocardiology 2004*. Vol 68. WORLD SCIENTIFIC; 2005:42-46.
- 31. Leong-Sit P, Zado E, Callans DJ, et al. Efficacy and Risk of Atrial Fibrillation Ablation Before 45 Years of Age. *Circ Arrhythmia Electrophysiol.* 2010;3(5):452-457.
- 32. Friberg L, Hammar N, Ringh M, et al. Stroke prophylaxis in atrial fibrillation: who gets it and who does not? *Eur Heart J.* 2006;27(16):1954–1964.
- 33. Ogilvie I, Newton N, Welner S, et al. Underuse of Oral Anticoagulants in Atrial Fibrillation: A Systematic Review. *Am J Med.* 2010;123(7):638-645.e4.
- 34. Hung Y, Chao T, Liu C, et al. Is an Oral Anticoagulant Necessary for Young Atrial Fibrillation Patients With a CHA 2 DS 2 -VASc Score of 1 (Men) or 2 (Women)? *J Am Heart Assoc.* 2016;5(10):1–8.
- 35. Coppens M, Eikelboom J, Hart R, et al. The CHA2DS2-VASc score identifies those patients with atrial fibrillation and a CHADS2 score of 1 who are unlikely to benefit from oral anticoagulant therapy. *Eur Heart J*. 2013;34(3):170–176.
- 36. Sionis A, Sionis G, Manito L, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Rev Española Cardiol (English Ed.* 2016;69(12):1119–1125.
- 37. Gage B, Waterman A, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation (NRAF). *JAMA*. 2001;285(22):2864–2870.
- 38. Lip G, Nieuwlaat R, Pisters R, et al. Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach. The Euro Heart Survey on Atrial Fibrillation. *Chest.* 2010;137(2):263–272.
- 39. Olesen J, Fauchier L, Lane D, et al. Risk Factors for Stroke and Thromboembolism in Relation to Age Among Patients With Atrial Fibrillation. *Chest.* 2012;141(1):147–153.