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Atrial Fibrillation Diagnosis using ECG Records and Self-Report in the Community: Cross-Sectional Analysis from ELSA-Brasil

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Abstract

Background: **Atrial fibrillation or flutter (AFF) is the most common sustained cardiac arrhythmia. Limited data can be found on AFF epidemiology in South America.**

Objective: **The present study sought to describe the clinical epidemiology of AFF and the use of stroke prevention medication in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) baseline assessment.**

Methods: **This study analyzed data from 13,260 ELSA-Brasil participants. AFF was defined according to ECG recording or by self-report. Logistic regression models were built to analyze factors associated with AFF. This study also analyzed if age and sex were associated with anticoagulant use for stroke prevention. Significance level was set at 5%.**

Results: **Median age was 51 years and 7,213 (54.4%) participants were women. AFF was present in 333 (2.5%) participants. Increasing age (odds ratio [OR]:1.05; 95% confidence interval [95%CI]: 1.04–1.07), hypertension (OR:1.44; 95%CI: 1.14–1.81), coronary heart disease (OR: 5.11; 95%CI: 3.85–6.79), heart failure (OR:7.37; 95%CI: 5.00–10.87), and rheumatic fever (OR:3.38; 95%CI: 2.28–5.02) were associated with AFF. From 185 participants with AFF and a CHA2DS2-VASc score ≥2, only 20 (10.8%) used anticoagulants (50.0% among those with AFF in the baseline ECG). Stroke prevention in this group was associated with a higher age (1.8% vs 17.7% in those aged ≤ 54 and ≥ 65 years, respectively; p=0.013). A trend towards a reduced anticoagulant use was observed in women (7.1% vs. 16.4% in women and men, respectively; p=0.055).**

Conclusions: **At the ELSA-Brasil baseline, 2.5% of the participants had AFF. The lack of stroke prevention was common, which is an especially challenging point for healthcare in this setting.**

Keywords: **Atrial Fibrillation; Epidemiology; Electrocardiography/methods; Anticoagulants; Longitudinal Study; Aged; Stroke; Embolism.**

Introduction

Atrial fibrillation is the most prevalent sustained cardiac arrythmia, with an approximate lifetime risk of 25%[1] and an estimated 33.3 million prevalent cases globally.[2] In São Paulo, Brazil, a population-based study[3] found that 3.2% of men and 2.0% of women aged 65 years or older had atrial fibrillation. Another large database of primary care patients aged 5 years or older (71% aged ≥ 40 years) in Minas Gerais, Brazil,[4] found that 2.4% of men and 1.3% of women had atrial fibrillation. Risk factors for atrial fibrillation or flutter include age, hypertension, diabetes, smoking, obesity, heart failure, valve disease, and myocardial infarction.[5-7]

Risk-based thromboembolic (including stroke) prevention therapy is recommended for patients with atrial fibrillation or flutter (AFF).[8,9] The CHA_2DS_2-VASc scores[10] are currently the main strategy to evaluate thromboembolic risk in these individuals.[11] Oral antithrombotic therapy is recommended for those with a CHA_2DS_2-VASc score ≥ 2.[9]

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Oral anticoagulation therapy, however, still represents a challenge in clinical practice,[12,13] and a significant proportion of AFF disease burden is still associated with incident stroke,[14] especially in women.[15,16] This is even more important in Brazil, where although age-adjusted incident rates of stroke in the country have been falling in recent years,[17] stroke mortality is still high when compared to other South American countries, with a higher impact on the less developed states of the nation.[17,18]

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a large multicenter cohort of individuals of 35 to 74 years of age in six Brazilian cities, whose aim is to study the incidence and associated factors for cardiovascular diseases and diabetes. The objectives of the present study are to describe the frequency of AFF at the ELSA-Brasil baseline and the use of stroke prevention medication in participants with AFF and a CHA_2DS_2-VASc score ≥ 2.

Methods

Study setting and design

The ELSA-Brasil design[19] and cohort profile[20] are detailed elsewhere. Briefly, ELSA-Brasil is a cohort study of 15,105 civil servants from six Brazilian cities (São Paulo, Belo Horizonte, Porto Alegre, Salvador, Rio de Janeiro, and Vitoria). Baseline assessments took place from August 2008 to December 2010 and included in-person interviews conducted by trained personnel, using clinical, laboratory, and imaging exams. Since baseline, all participants receive a yearly telephone follow-up contact. Four years after enrollment (2012-2014), all participants were invited to undergo onsite reassessment, which included new questionnaires, and clinical and laboratory evaluations. This reassessment was attended by 14,014 (92.8%) participants. Informed consent was obtained from all participants. Study protocol is in accordance to the Brazilian National Health Council 466/2012 resolution and was approved by the Institutional Review Board in each participating center.

Atrial fibrillation or flutter diagnosis

Methods to record electrocardiographic (ECG) tracings in ELSA-Brasil are detailed elsewhere.[21] ECG at the baseline was performed in each center, using a Burdick Atria 6100 device, calibrated at 10 mm/mV and a speed of 25 mm/second. The recordings were transmitted to the reading center in Minas Gerais Investigation Center. Analyses followed the Glasgow system,[22] and were coded according to the Minnesota Coding System. Selected codes (including AFF) were manually reviewed by trained staff. In addition, in the onsite reassessment conducted in 2012-2014, participants were asked the following question: *"Did a physician ever say that you have/had atrial fibrillation?"* Participants who answered "yes" to that question were asked *"How old were you the first time a physician told you that you have/had atrial fibrillation?"*

The present study defined AFF diagnosis at the baseline if the participant (a) had an ECG recording with AFF in the ELSA-Brasil baseline assessment (n=48) or (b) indicated that they have had an atrial fibrillation diagnosis at an age lower than his/her age upon ELSA-Brasil enrollment (n=285). Most analyses are presented for all AFF cases and according to each definition criterion.

Study sample

This study included ELSA-Brasil participants for whom AFF diagnosis at the baseline could be assessed. From the 15,105 ELSA-Brasil participants, 663 (4.4%) participants were excluded because they did not have a valid ECG reading at the baseline nor a valid answer for the AFF in the 2012-2014 onsite reassessment, and 1,182 (7.8%) were excluded because they had a valid ECG reading at the baseline without AFF, but without a valid answer for the AFF in the 2012-2014 onsite reassessment (impairing the assessment of paroxysmal AFF). Therefore, our main sample consisted of 13,260 (87.8%) participants.

Other variables

Age, sex, race, level of education, monthly family income, and smoking status were self-reported and stratified accordingly. Monthly income was transformed into US dollars (using a conversion rate of BRL 2.00=USD 1.00, based on the exchange rate at the baseline). Race was defined, as adopted by the Brazilian National Census, as Black, Mixed, White, Asian, and Native (Indigenous). The anthropometric measurements in the ELSA-Brasil were assessed using standard techniques,[23] and body mass index (BMI) was calculated by dividing weight by height squared. BMI was categorized as normal (< 25 kg/m²), overweight (≥ 25 kg/m² and < 30 kg/m²), and obese (≥ 30 kg/m²). Hypertension was defined as the report of the use of medications to treat hypertension, a systolic blood pressure ≥ 140 mmHg, or a diastolic blood pressure ≥ 90 mmHg upon ELSA-Brasil baseline assessment. Diabetes was defined as a medical history of diabetes mellitus, the report of the use of medications to treat diabetes mellitus, a fasting serum glucose ≥ 126 mg/dl, HbA1c levels ≥ 6.5%, or a 2-h oral glucose tolerance test ≥ 200 mg/dl. Dyslipidemia was defined as the report of the use of lipid lowering treatment or an LDL cholesterol level ≥ 130 mg/dl. Abdominal obesity was defined as a waist circumference > 88 cm in women and > 102 cm in men. Previous medical diagnosis of heart failure, stroke, rheumatic fever, and thromboembolic event were assessed by self-report. Coronary artery disease was defined by a previous medical diagnosis of myocardial infarction or angina pectoris or by previous coronary revascularization. Ankle and brachial pressure measurements for ankle-brachial index (ABI) calculation is described in detail in Miname et al.[24]. According to the findings of that study, ABI was calculated as the ratio between the minimum leg systolic pressure and the maximum arm systolic pressure for higher sensitivity. Peripheral artery disease was defined as an ABI < 1.0.[24,25] For medication use data, other than questionnaires, patients were asked to bring to the baseline assessment of all medications and prescription drugs they were currently taking.[26] Use of anticoagulants was defined by using a medication under Anatomical Therapeutic Chemical (ATC) codes B01AA or B01AB. Use of antiplatelet agents was defined by using a medication under ATC code B01AC. For participants without previous coronary artery disease or stroke, 10-year atherosclerotic cardiovascular

disease (ASCVD) risk was calculated according to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.[27] CHA_2DS_2-VASc scores were calculated according to Lip et al.[11] and categorized as 0 or 1 point, 2 or 3 points, and ≥ 4 points.

Statistical analysis

Categorical variables are presented as counts and proportions, and were compared using Chi-squared or Fisher's exact tests. Continuous variables (age, body-mass index, ankle-brachial index and 10-year ASCVD risk) have non-normal distribution ($p<0.001$ for all, using the Anderson-Darling test), and are presented as medians and interquartile ranges and compared among groups using Mann-Whitney U tests. Crude and age- and sex-adjusted logistic regression models were built to analyze if AFF diagnosis at the ELSA-Brasil baseline was associated with age, sex, race, level of education, monthly income, smoking status, hypertension, diabetes and dyslipidemia diagnoses, BMI, abdominal obesity, peripheral artery disease, coronary heart disease, heart failure, stroke, rheumatic fever, and a 10-year CHD risk > 10%. Binary logistic regression was used to analyze the association with all AFF cases, while multinomial logistic regression was used to analyze the association with AFF cases according to each definition criterion (by ECG recording or self-report) in separate. The significance level was set at 5%, and R software, version 3.5.1, was used in all analyses.

Results

Among the 13,260 participants included in the analyses, 333 (2.5%) had AFF at the ELSA-Brasil baseline, 176/7,213 (2.4%) women and 157/6,047 (2.6%) men. According to age strata, the frequency of AFF diagnosis was 1.2%, 2.2%, 2.9%, and 5.4% for ages < 45, 45-54, 55-64, and > 64 years, respectively. Table 1 shows the study's sample characteristics, according to the presence of AFF diagnosis at the ELSA-Brasil baseline. Individuals of non-white races represented 47.9% of the sample, and most participants had a college degree or higher education.

Table 2 shows crude and age- and sex-adjusted odds ratios for the association with the presence of AFF diagnosis at the ELSA-Brasil baseline. Considering all AFF cases, higher age ($p<0.001$), higher income ($p=0.044$), hypertension ($p=0.002$), coronary heart disease ($p<0.001$), heart failure ($p<0.001$), and rheumatic fever diagnoses ($p<0.001$) were positively associated with AFF in the adjusted models. Restricting the cases to the 48 participants who presented AFF in the baseline ECG, higher age ($p<0.001$), male sex ($p=0.037$), peripheral artery disease ($p=0.026$), heart failure ($p<0.001$), and rheumatic fever diagnoses ($p<0.001$) were positively associated with AFF in the adjusted models. Supplemental Table 1 shows crude model results for these associations.

CHA_2DS_2-VASc scores could be calculated for 331 (99.4%) of the 333 participants with AFF diagnosis at the baseline (Table 3). As expected, individuals with higher CHA_2DS_2-VASc scores were older ($p<0.001$), were more likely to be women ($p=0.002$), and presented a higher cardiovascular risk ($p<0.001$). Among 185 participants with a CHA_2DS_2-VASc score ≥ 2, only 20 (10.8%) received anticoagulant therapy (16/32; 50.0% when restricting cases to the 48 participants who presented AFF in the baseline ECG).

Table 4 shows the prevalence of oral anticoagulant use in participants with AFF and a CHA_2DS_2-VASc score ≥ 2, according to age and sex. Considering all AFF cases, anticoagulant use was more frequent in those with a higher age ($p=0.013$), and a trend towards lower anticoagulant use in women ($p=0.055$). Supplemental table 2 shows that the frequency of anticoagulant use in men was numerically higher than in women for all age strata, but no significant differences were discovered when analyzing all AFF cases nor when restricting them to those participants who presented with AFF in the baseline ECG.

Discussion

Contextualization and discussion of main findings

In our cohort sample, 2.5% of the included participants presented AFF at the baseline. Age, male sex, income, hypertension, coronary heart disease, peripheral artery disease, heart failure, and rheumatic fever diagnoses were positively associated with AFF. Second, most participants with AFF and a CHA_2DS_2-VASc score ≥ 2 did not receive anticoagulants and/or antiplatelet agents. Third, oral anticoagulant use was more common in those with a higher age, while women were less commonly treated.

Comparing AFF prevalence across samples is challenging because of differences in study design, study setting, and age and sex distribution upon recruitment. A review of the global epidemiology of atrial fibrillation[28] found a reported worldwide prevalence ranging from 0.1% to 6.0%, depending on the age strata and sex analyzed. Although this study reports a similar frequency of AFF diagnosis in the sample when compared to the cited Brazilian studies,[3,4] these studies have marked differences and are complementary. For example, Kawabata-Yoshihara et al.[3] performed a systematic door knock of individuals 65 years of age or older, while Marcolino et al.[4] used a large ECG database from the Telehealth Network of Minas Gerais consisting of individuals 5 years of age or older who received medical care in primary care units. Both studies considered AFF diagnosis according to ECG recordings upon assessment. When comparing the findings from those studies to the findings from the present study, a higher frequency of AFF was found when similar age strata are compared. This is most likely influenced by case definitions, as the present study also included a self-reported medical diagnosis as a diagnostic criterion. However, considering only the ECG tracings during assessment and excluding medical history from case definitions may yield the highest specificity and reduce self-reported information error, but it can also underestimate prevalence rates due to the under-recognition of paroxysmal atrial fibrillation.

The association between heart failure and atrial fibrillation has clinical importance. Healey et al.[12] analyzed data from 15,400 individuals with AFF in 47 countries. After one year of follow-up, death occurred in 11% of the cohort, and heart

Table 1 – Study sample characteristics according to the presence of atrial fibrillation or flutter in the ELSA-Brasil baseline

	No atrial fibrillation or flutter (N=12,927)	Atrial fibrillation or flutter			Total (N=13,260)	p-value
		By ECG recording (N=48)	By self-report only (N=285)	All AFF cases (N=333)		
Age (years; median [P25 - P75])	51.0 [45.0 – 58.0]	61.5 [56.0 – 71.0]	54.0 [49.0 – 62.0]	56.0 [49.0 – 63.0]	51.0 [45.0 – 58.0]	<0.001 ‡
Female sex (N (%))	7.037 (54.4%)	18 (37.5%)	158 (55.4%)	176 (52.9%)	7.213 (54.4%)	0.61 †
Race (N (%))						
White	6.652 (52.1%)	29 (61.7%)	154 (54.6%)	183 (55.6%)	6.835 (52.1%)	0.039 †
Mixed	3.608 (28.2%)	11 (23.4%)	74 (26.2%)	85 (25.8%)	3.693 (28.2%)	
Black	2.069 (16.2%)	7 (14.9%)	35 (12.4%)	42 (12.8%)	2.111 (16.1%)	
Other	449 (3.5%)	0 (0.0%)	19 (6.7%)	19 (5.8%)	468 (3.6%)	
Level of education (N (%))						
Up to incomplete high school	1.529 (11.8%)	13 (27.1%)	34 (11.9%)	47 (14.1%)	1.576 (11.9%)	0.10 †
High school	4.443 (34.4%)	12 (25.0%)	85 (29.8%)	97 (29.1%)	4.540 (34.2%)	
College or above	6.955 (53.8%)	23 (47.9%)	166 (58.2%)	189 (56.8%)	7.144 (53.9%)	
Monthly income (N (%))						
<USD1245	3.357 (26.1%)	15 (31.2%)	58 (20.4%)	73 (22.0%)	3.430 (26.0%)	0.001 †
USD1245-3319	5.679 (44.1%)	12 (25.0%)	115 (40.5%)	127 (38.3%)	5.806 (43.9%)	
≥ USD3320	3.845 (29.9%)	21 (43.8%)	111 (39.1%)	132 (39.8%)	3.977 (30.1%)	
Smoking status (N (%))						
Never smoked	7.467 (57.8%)	29 (60.4%)	161 (56.5%)	190 (57.1%)	7.657 (57.7%)	0.75 †
Past smoker	3.822 (29.6%)	13 (27.1%)	91 (31.9%)	104 (31.2%)	3.926 (29.6%)	
Current smoker	1.637 (12.7%)	6 (12.5%)	33 (11.6%)	39 (11.7%)	1.676 (12.6%)	
Hypertension (N (%))	4.463 (34.5%)	30 (62.5%)	136 (47.7%)	166 (49.8%)	4.629 (34.9%)	<0.001 †
Diabetes (N (%))	2.438 (18.9%)	15 (31.2%)	66 (23.2%)	81 (24.3%)	2.519 (19.0%)	0.015 †
Dyslipidemia (N (%))	7.489 (58.0%)	27 (56.2%)	188 (66.0%)	215 (64.6%)	7.704 (58.1%)	0.019 †
Body-mass index (kg/m2; median [P25 - P75])	26.3 [23.7 – 29.5]	27.4 [25.4 – 30.4]	26.2 [23.9 – 30.2]	26.5 [24.1 – 30.3]	26.3 [23.7 – 29.6]	0.35 ‡
Body-mass index classification (N (%))						
Normal	4.791 (37.1%)	10 (20.8%)	104 (36.5%)	114 (34.2%)	4.905 (37.0%)	0.057 †
Overweight	5.238 (40.5%)	24 (50.0%)	102 (35.8%)	126 (37.8%)	5.364 (40.5%)	
Obese	2.892 (22.4%)	14 (29.2%)	79 (27.7%)	93 (27.9%)	2.985 (22.5%)	
Abdominal obesity (N (%))	4.656 (36.0%)	20 (41.7%)	113 (39.6%)	133 (39.9%)	4.789 (36.1%)	0.16 †
Ankle-brachial index (median [P25 - P75])	1.18 [1.12 – 1.23]	1.13 [1.04 – 1.20]	1.17 [1.11 – 1.24]	1.16 [1.10 – 1.23]	1.18 [1.12 – 1.23]	0.008 ‡
Peripheral artery disease (N (%))	403 (3.1%)	6 (12.5%)	12 (4.2%)	18 (5.4%)	421 (3.2%)	0.025 †
Use of anticoagulants (N (%))	37 (0.3%)	19 (39.6%)	5 (1.8%)	24 (7.2%)	61 (0.5%)	<0.001 †
Use of antiplatelet agents (N (%))	706 (5.5%)	7 (14.6%)	45 (15.8%)	52 (15.6%)	758 (5.7%)	<0.001 †
Use of anticoagulant and/or antiplatelet agents (N (%))	741 (5.7%)	26 (54.2%)	50 (17.5%)	76 (22.8%)	817 (6.2%)	<0.001 †
Coronary artery disease (N (%))	536 (4.2%)	7 (14.6%)	67 (23.5%)	74 (22.2%)	610 (4.6%)	<0.001 †
Heart failure (N (%))	160 (1.2%)	10 (20.8%)	26 (9.2%)	36 (10.8%)	196 (1.5%)	<0.001 †
Stroke (N (%))	153 (1.2%)	1 (2.1%)	7 (2.5%)	8 (2.4%)	161 (1.2%)	0.067 †
Rheumatic fever (N (%))	352 (2.7%)	7 (14.6%)	23 (8.1%)	30 (9.0%)	382 (2.9%)	<0.001 †
Thromboembolic event (N (%))	198 (1.5%)	4 (8.3%)	5 (1.8%)	9 (2.7%)	207 (1.6%)	0.11 †
10-year ASCVD risk (median [P25 - P75])	2.8% [1.1% -7.1%]	11.8% [4.2% – 18.5%]	2.7% [1.4% – 7.9%]	3.4% [1.5% - 10.4%]	2.8% [1.1% – 7.2%]	0.001 ‡
10-year ASCVD risk > 10% (N (%))	2075 (16.9%)	23 (57.5%)	41 (19.2%)	64 (25.2%)	2139 (17.1%)	0.001 †

The 10-year ASCVD risk is defined only in participants without prior coronary artery disease or stroke. AFF: Atrial fibrillation or flutter. ASCVD: Atherosclerotic cardiovascular disease. P-values are presented for the comparison between the no atrial fibrillation or flutter (N=12,927) and all AFF case (N=333) groups, using † Chi-squared or ‡ Mann-Whitney U tests

Table 2 – Age- and sex-adjusted odds ratios (95% CIs) for the association with atrial fibrillation or flutter in the ELSA-Brasil baseline

	Atrial fibrillation or flutter		
Variable	**By ECG recording (N=48)**	**By self-report only (N=285)**	**All AFF cases (N=333)**
Age (one-year increase)	1.12 [1.09 – 1.16]	1.04 (1.03 – 1.06) †	1.05 (1.04 – 1.07) †
Female sex	0.53 (0.30 – 0.96) †	1.05 (0.83 – 1.33)	0.95 (0.76 – 1.18)
Race*			
White	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Mixed	0.92 (0.45 – 1.85)	0.95 (0.72 – 1.26)	0.94 (0.72 – 1.22)
Black	(0.43 – 2.27)	0.76 (0.52 – 1.10)	0.79 (0.56 – 1.10)
Level of education			
Up to incomplete high school	1.73 (0.87 – 3.43)	0.79 (0.54 – 1.15)	0.92 (0.66 – 1.27)
High school	1.12 (0.55 – 2.28)	0.86 (0.66 – 1.12)	0.88 (0.69 – 1.13)
College or above	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Monthly income			
<USD1245	1.27 (0.64 – 2.51)	0.67 (0.48 – 0.93) †	0.74 (0.55 – 0.99) †
USD1245-3319	0.61 (0.29 – 1.25)	0.80 (0.61 – 1.04)	0.77 (0.60 – 0.99) †
≥ USD3320 (N (%))	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Smoking status			
Never smoked	(Reference)	(Reference)	1.0 (Reference)
Past smoker	0.57 (0.29 - 1.12)	0.98 (0.75 – 1.27)	0.90 (0.70 – 1.16)
Current smoker	1.00 (0.42 – 2.40)	0.93 (0.64 – 1.36)	0.93 (0.65 – 1.32)
Hypertension	1.65 (0.89 – 3.03)	1.41 (1.10 – 1.81) †	1.44 (1.14 – 1.81) †
Diabetes	1.11 (0.60 – 2.08)	1.06 (0.80 – 1.41)	1.07 (0.82 – 1.39)
Dyslipidemia	0.66 (0.37 – 1.18)	1.22 (0.95 – 1.57)	1.10 (0.87 – 1.39)
Body-mass index classification			
Normal	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Overweight	1.88 (0.90 – 3.95)	0.85 (0.64 – 1.12)	0.94 (0.72 – 1.21)
Obese	2.21 (0.97 – 5.00)	1.19 (0.88 – 1.60)	1.27 (0.96 – 1.68)
Abdominal obesity	1.15 (0.63 – 2.08)	1.04 (0.81 – 1.33)	1.05 (0.83 – 1.32)
Peripheral artery disease	2.72 (1.13 – 6.54) †	1.16 (0.64 – 2.10)	1.44 (0.88 – 2.35)
Coronary artery disease	1.87 (0.81 – 4.28)	5.99 (4.44 – 8.09) †	5.11 (3.85 – 6.79) †
Heart failure	11.67 (5.58 – 24.40) †	6.51 (4.19 – 10.11) †	7.37 (5.00 – 10.87) †
Stroke	0.90 (0.12 – 6.67)	1.65 (0.76 – 3.57)	1.51 (0.73 – 3.13)
Rheumatic fever	5.75 (2.55 – 12.98) †	3.02 (1.94 – 4.70) †	3.38 (2.28 – 5.02) †
10-year ASCVD risk > 10%	1.56 (0.63 – 3.85)	0.78 (0.50 – 1.21)	0.95 (0.65 – 1.40)

**The small proportion of individuals of other races in the sample precluded estimation. AFF: Atrial fibrillation or flutter. ASCVD: Atherosclerotic cardiovascular disease. Odds ratios and p-values were obtained from logistic regression models adjusted for age and sex. †p<0.05.*

failure was the most common cause of death (30%). Similarly, individuals with peripheral artery disease and AFF have a higher risk of stroke when compared to those with only AFF.[29] It is important to note that, in recent decades, rheumatic heart disease has decreased as a cause of mortality in Brazil,[30] and although new cases in the country are less common, current middle-aged and older adults may have had rheumatic fever during childhood. Therefore, the prevalence and mortality due to rheumatic heart disease in Brazil is not negligible,[31] which is reinforced by our finding that 9.0% of the individuals with AFF in this study's sample (and 2.9% overall) presented a medical history of rheumatic fever.

A striking finding of the present study was that 89.2% of all participants with AFF and a CHA_2DS_2-VASc score ≥ 2 did not receive anticoagulants. This is more important considering that ELSA-Brasil participants have a higher mean level of education and income when compared to the general Brazilian population.[20] Although self-reported diagnoses may

Table 3 – Characteristics of participants with atrial fibrillation or flutter in the ELSA-Brasil baseline according to CHA_2DS_2-VASc scores

	Atrial fibrillation or flutter						
	By ECG recording		By self-report only		All AFF cases		
	CHA_2DS_2-VASc score < 2 (N=16)	CHA_2DS_2-VASc score ≥ 2 (N=32)	CHA_2DS_2-VASc score < 2 (N=130)	CHA_2DS_2-VASc score ≥ 2 (N=153)	CHA_2DS_2-VASc score < 2 (N=146)	CHA_2DS_2-VASc score ≥ 2 (N=185)	p-value
Age (years; median [P25 - P75])	56.0 [49.5 – 61.2]	67.5 [58.0 – 71.2]	49.5 [45.0 – 56.0]	59.0 [53.0 – 66.0]	50.0 [45.0 – 57.0]	60.0 [53.0 – 68.0]	<0.001 ‡
Female sex (N (%))	3 (18.8%)	15 (46.9%)	60 (46.2%)	97 (63.4%)	63 (43.2%)	112 (60.5%)	0.002 †
Coronary artery disease (N (%))	0 (0.0%)	7 (21.9%)	2 (1.5%)	64 (41.8%)	2 (1.4%)	71 (38.4%)	<0.001 †
Stroke (N (%))	0 (0.0%)	1 (3.1%)	0 (0.0%)	7 (4.6%)	0 (0.0%)	8 (4.3%)	0.010 ¥
10-year ASCVD risk > 10% (N (%))	7 (43.8%)	16 (66.7%)	15 (11.7%)	26 (30.6%)	22 (15.3%)	42 (38.5%)	<0.001 †
Prior ASCVD or 10-year ASCVD risk > 10%	7 (43.8%)	24 (75.0%)	17 (13.1%)	94 (61.4%)	24 (16.4%)	118 (63.8%)	<0.001 †
Use of anticoagulants (N (%))	3 (18.8%)	16 (50.0%)	1 (0.8%)	4 (2.6%)	4 (2.7%)	20 (10.8%)	0.005 ¥
Use of antiplatelet agents (N (%))	2 (12.5%)	5 (15.6%)	2 (1.5%)	43 (28.1%)	4 (2.7%)	48 (25.9%)	<0.001 †

The 10-year ASCVD risk is defined only in participants without prior coronary artery disease or stroke. AFF: Atrial fibrillation or flutter. ASCVD: Atherosclerotic cardiovascular disease. P-values are presented for the comparison between the CHA2DS2-VASc score < 2 (N=146) and the CHA2DS2-VASc score ≥ 2 (N=185) groups among all AFF cases using † Chi-squared, ‡ Mann-Whitney U or ¥ Fisher's exact tests

Table 4 – Frequency of anticoagulant use according to age and sex in participants with atrial fibrillation or flutter and a CHA_2DS_2-VASc score ≥ 2 in the ELSA-Brasil baseline

	Atrial fibrillation or flutter and a CHA_2DS_2-VASc score ≥ 2			
Variable	By ECG recording (N=32)	By self-report only (N=153)	All AFF cases (N=185)	p-value
Age (years)				
≤ 54	1 / 3 (33.3%)	0 / 52 (0.0%)	1 / 55 (1.8%)	0.013
55 – 64	6 / 11 (54.5%)	2 / 57 (3.5%)	8 / 68 (11.8%)	
≥ 65	9 / 18 (50.0%)	2 / 44 (4.5%)	11 / 62 (17.7%)	
Sex				
Male	9 / 17 (52.9%)	3 / 56 (5.4%)	12 / 73 (16.4%)	0.055
Female	7 / 15 (46.7%)	1 / 97 (1.0%)	8 / 112 (7.1%)	

The frequency of anticoagulant use according to age and sex, considering all AFF cases with a CHA_2DS_2-VASc score ≥ 2 was compared using Fisher's exact tests.

have influenced our finding of low rates of stroke prevention, when we limited analyses to participants with a documented AFF in the baseline ECG recording, half of them still had not received anticoagulants.

Although concerning, these low stroke prevention prescription rates are not exclusive to our sample. A similar study conducted by Healey et al.[12] described that, by geographic region, 32% (North America, Western Europe, Australia, and the Middle East) to 70% (China) guideline-indicated patients did not receive oral anticoagulant therapy. In South America, where ELSA-Brasil is located, the frequency of non-prescription was 55%. Ogilvie et al.[32] reported a systematic review of studies reporting the use of oral anticoagulants in atrial fibrillation outside of clinical trials. They found that 21/29 (72.4%) studies in patients with prior stroke or transient ischemic attack, as well as 5/9 (55.6%) studies in patients with high thromboembolic risk according to risk scores, reported prescriptions levels of below 60%.

The under-prescription of stroke prevention medication seems to be a more severe problem in women,[33] which is in accordance with our data. Khurshid et al.[34] analyzed electronic medical data from 4,388 patients with atrial fibrillation and found that women, when compared to men, received less anticoagulant therapy at 1, 3, and 6 months after atrial

fibrillation diagnosis. In addition, Emdin et al.[35] performed a systematic review and meta-analysis of 30 cohort studies and found that women, as compared to men, with atrial fibrillation had a higher risk of all-cause mortality, cardiovascular mortality, and stroke. These authors highlight that, besides the underuse of stroke prevention medication, other explanations for worse outcomes, such as the higher rates of adverse effects from anticoagulant[36] and antiarrhythmic[37] therapies in women are equally plausible. In addition, some authors have highlighted worse anticoagulation control in women receiving warfarin. For example, Sullivan et al.[38] analyzed data from 4,060 participants of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, and found that women, as compared to men, on warfarin spent significantly more time below the international normalized ratio (INR) therapeutic range (29% vs 26%). It is also important to note that, the ELSA-Brasil baseline assessment occurred from 2008 to 2010. At that time, the use of direct-acting oral anticoagulants for stroke prevention in AFF was very rare.

Strengths and limitations

This study does have some strengths. We analyzed data from a large, multicenter sample of individuals who were not recruited from clinical settings. This reduces potential biases in the study of factors associated with atrial fibrillation and diagnosis and the prescription of stroke prevention medications, approximating our external validity to the general population. The comprehensive ELSA-Brasil protocol allowed for the analysis of medication use according to CHA_2DS_2-VASc thromboembolic risk scores. This study must also be interpreted within its context. As stated earlier, this study's case definition may be prone to self-reported information misclassifications. Although this strategy minimizes the under-recognition of paroxysmal atrial fibrillation, it is important to acknowledge that self-reported cases were an important proportion of all AFF cases, and this may have influenced some of our results. Data on the frequency of individuals within the INR therapeutic range or on bleeding risk scores was not available. However, we believe that the risk of high bleeding is unable to explain a substantial part of the lack of stroke prevention in this sample.

Conclusions

In conclusion, a 2.5% frequency of AFF diagnosis was found at the ELSA-Brasil baseline assessment. Age, male sex, peripheral artery disease, heart failure, or rheumatic fever diagnoses were associated with AFF. Almost 90% of the subsample of participants with AFF and a CHA_2DS_2-VASc score ≥ 2 (50% considering only those diagnosed by ECG records) did not receive anticoagulants.

Author Contributions

Conception and design of the research: Santos I S, Lotufo P A, Barreto SM, Ribeiro AL, Bensenor I M; Acquisition of data: Lotufo P A, Brant L, Pinto-Filho MM, Barreto SM, Ribeiro AL, Bensenor I M; Analysis and interpretation of the data: Santos I S, Lotufo P A, Brant L, Pinto-Filho MM, Pereira AC, Barreto SM, Ribeiro AL, Thomas GN, Lip GYH, Bensenor I M; Statistical analysis: Santos I S; Obtaining financing: Lotufo P A, Barreto SM, Ribeiro AL, Bensenor I M; Writing of the manuscript: Santos I S, Bensenor I M; Critical revision of the manuscript for intellectual contente: Lotufo P A, Brant L, Pinto-Filho MM, Pereira AC, Barreto SM, Ribeiro AL, Thomas GN, Lip GYH.

Potential Conflict of Interest

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

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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 Hospital Universitário da USP under the protocol number 659/06. 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.

References

1. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004;110(9):1042-6.
2. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25.
3. Kawabata-Yoshihara LA, Scazufca M, Santos IS, Whitaker A, Kawabata VS, Benseñor IM, et al. Atrial fibrillation and dementia: results from the Sao Paulo ageing & health study. Arq Bras Cardiol. 2012;99(6):1108-14.
4. Marcolino MS, Palhares DM, Benjamin EJ, Ribeiro AL. Atrial fibrillation: prevalence in a large database of primary care patients in Brazil. Europace. 2015;17(12):1787-90.
5. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271(11):840-4.
6. Norby FL, Soliman EZ, Chen LY, Bengtson LG, Loehr LR, Agarwal SK, et al. Trajectories of cardiovascular risk factors and incidence of atrial fibrillation over a 25-year follow-up: the ARIC Study (Atherosclerosis Risk in Communities). Circulation. 2016;134(8):599-610.

7. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009;373(9665):739-45.

8. Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. Thromb Haemost. 2017;117(7):1230-9.

9. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018;154(5):1121-201.

10. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation. 2012;126(7):860-5.

11. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. 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):263-72.

12. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet. 2016;388(10050):1161-9.

13. Lotufo PA. Stroke prevention within primary care: management of atrial fibrillation using oral anticoagulation. Sao Paulo Med J. 2018;136(4):273-5.

14. Nakayama T, Yokoyama T, Yoshiike N, Zaman MM, Date C, Tanaka H, et al. Population attributable fraction of stroke incidence in middle-aged and elderly people: contributions of hypertension, smoking and atrial fibrillation. Neuroepidemiology. 2000;19(4):217-26.

15. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. Neuroepidemiology. 2003;22(2):118-23.

16. Iwahana H, Ishikawa S, Ishikawa J, Kabutoya T, Kayaba K, Gotoh T, et al. Atrial fibrillation is a major risk factor for stroke, especially in women: the Jichi Medical School cohort study. J Epidemiol. 2011;21(2):95-101.

17. Lotufo PA, Goulart AC, Passos VMA, Satake FM, Souza MFM, França EB, et al. Cerebrovascular disease in Brazil from 1990 to 2015: Global Burden of Disease 2015. Rev Bras Epidemiol. 2017 May;20(Suppl 01):129-41.

18. Lotufo PA. Stroke is still a neglected disease in Brazil. Sao Paulo Med J. 2015;133(6):457-9.

19. Aquino EM, Barreto SM, Bensenor IM, Carvalho MS, Chor D, Duncan BB, et al. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. Am J Epidemiol. 2012;175(4):315-24.

20. Schmidt MI, Duncan BB, Mill JG, Lotufo PA, Chor D, Barreto SM, et al. Cohort profile: longitudinal study of adult health (ELSA-Brasil). Int J Epidemiol. 2015;44(1):68-75.

21. Pinto MM, Brant LCC, Padilha-da-Silva JL, Foppa M, Lotufo PA, Mill JG, et al. Electrocardiographic findings in brazilian adults without heart disease: ELSA-Brasil. Arq Bras Cardiol. 2017;109(5):416-24.

22. Macfarlane PW. Evolution of the Glasgow program for computer-assisted reporting of electrocardiograms--1964/1998. Acta Cardiol. 1998;53(2):117-20.

23. Mill JG, Pinto K, Griep RH, Goulart A, Foppa M, Lotufo PA, et al. [Medical assessments and measurements in ELSA-Brasil]. Rev Saude Publica. 2013;47(Suppl 2):54-62.

24. Miname M, Bensenor IM, Lotufo PA. Different methods of calculating ankle-brachial index in mid-elderly men and women: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Braz J Med Biol Res. 2016;49(12):e5734.

25. Verberk WJ, Kollias A, Stergiou GS. Automated oscillometric determination of the ankle-brachial index: a systematic review and meta-analysis. Hypertens Res. 2012;35(9):883-91.

26. Chor D, Alves MG, Giatti L, Cade NV, Nunes MA, Molina MC, et al. Questionnaire development in ELSA-Brasil: challenges of a multidimensional instrument. Rev Saude Publica. 2013;47(Suppl 2):27-36.

27. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49-73.

28. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014;11(11):639-54.

29. Olesen JB, Lip GY, Lane DA, Køber L, Hansen ML, Karasoy D, et al. Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. Am J Med. 2012;125(8):826.e13-23.

30. Brant LCC, Nascimento BR, Passos VMA, Duncan BB, Benseñor IJM, Malta DC, et al. Variations and particularities in cardiovascular disease mortality in Brazil and Brazilian states in 1990 and 2015: estimates from the Global Burden of Disease. Rev Bras Epidemiol. 2017;20(Suppl 01):116-28.

31. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990-2015. N Engl J Med. 2017;377(8):713-22.

32. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010;123(7):638-45.e4.

33. Thompson LE, Maddox TM, Lei L, Grunwald GK, Bradley SM, Peterson PN, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation: a Report from the National Cardiovascular Data Registry (NCDR) PINNACLE Registry. J Am Heart Assoc. 2017;6(7):e005801.

34. Khurshid S, Weng LC, Hulme OL, Ellinor PT, Lubitz SA. Factors associated with anticoagulation delay following new-onset atrial fibrillation. Am J Cardiol. 2017;120(8):1316-21.

35. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ. 2016 Jan 19;532:h7013.

36. Alotaibi GS, Almodaimegh H, McMurtry MS, Wu C. Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? a sex-based meta-analysis. Thromb Res. 2013;132(2):185-9.

37. Wolbrette DL. Risk of proarrhythmia with class III antiarrhythmic agents: sex-based differences and other issues. Am J Cardiol. 2003;91(6A):39D-44D.

38. Sullivan RM, Zhang J, Zamba G, Lip GY, Olshansky B. Relation of gender-specific risk of ischemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from AFFIRM). Am J Cardiol. 2012;110(12):1799-802.

*Supplemental Materials

For additional information, please click here.