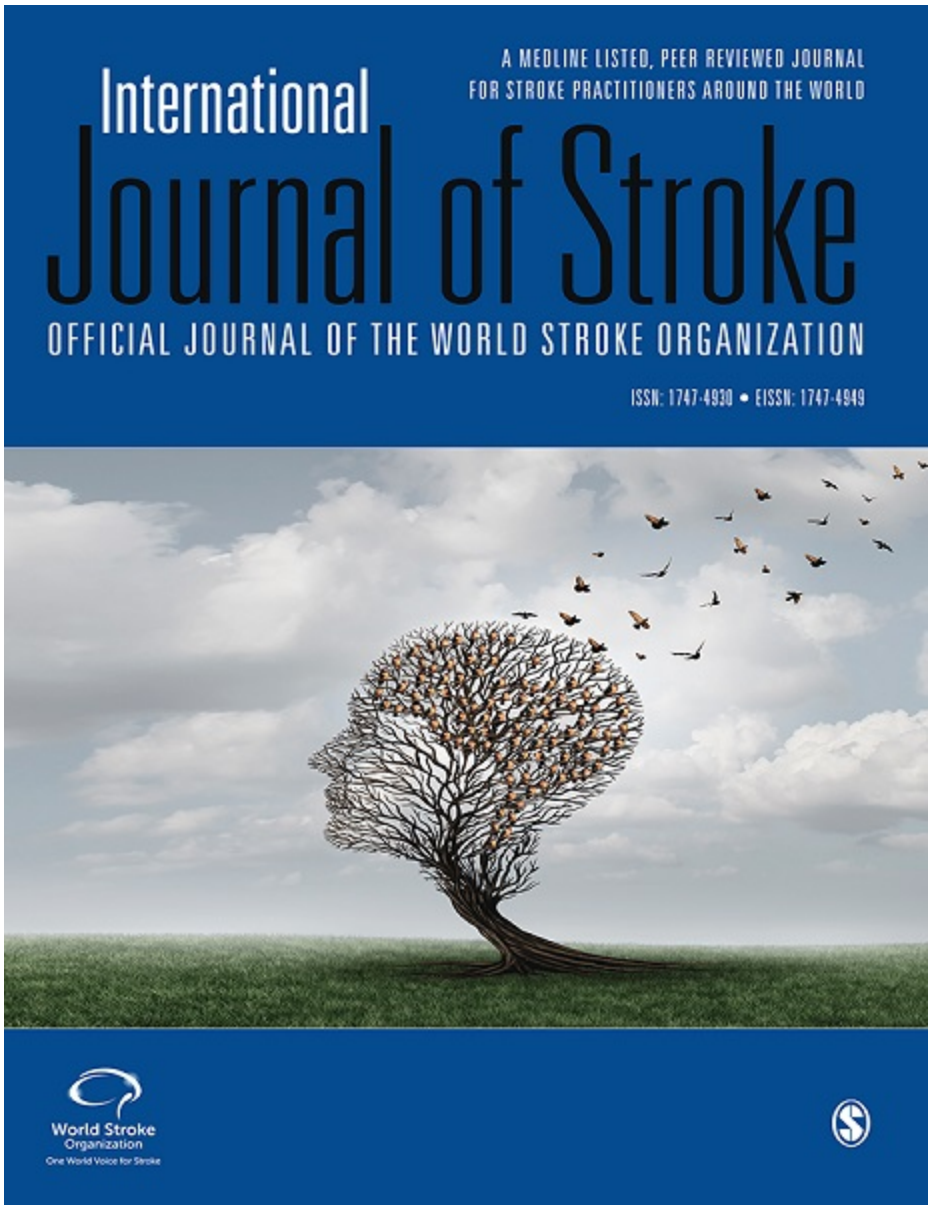
DOI: 10.1177/1747493021995592



The impact of atrial fibrillation and long-term oral anticoagulant use on all-cause and cardiovascular mortality: A 12-year evaluation of the prospective Brazilian Study of Stroke Mortality and Morbidity (EMMA)

Journal:	*International Journal of Stroke*
Manuscript ID	IJS-08-20-8408.R2
Manuscript Type:	Research

Date Submitted by the Author:	28-Dec-2020
Complete List of Authors:	Goulart, Alessandra; Universidade de Sao Paulo, Hospital Universitario; Universidade de Sao Paulo, Center for Clinical and Epidemiological Research, Hospital Universitário Olmos, Rodrigo; Universidade de Sao Paulo, Center for Clinical and Epidemiological Research, Hospital Universitario Santos, Itamar; Universidade de Sao Paulo, Center for Clinical and Epidemiological Research, Hospital Universitário Tunes, Gisela; Universidade de Sao Paulo, Institute of Mathematics and Statistics Alencar, Airlane; Universidade de Sao Paulo, Institute of Mathematics and Statistics Thomas, G. Neil; University of Birmingham, epartment of Public Health, Epidemiology and Biostatistics Lip, Gregory; University of Liverpool, Liverpool Centre for Cardiovascular Science Lotufo, Paulo; Universidade de Sao Paulo, Center for Clinical and Epidemiological Research, Hospital Universitario Bensenor, Isabela; Universidade de Sao Paulo Faculdade de Medicina, Center for Clinical and Epidemiological Research, Hospital Universitário
Keywords:	Treatment, Prevention, Developing countries, Risk factors, Ischaemic stroke, Neurology

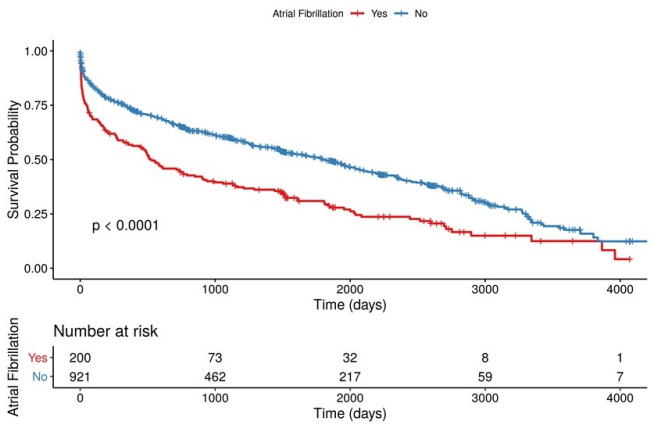


Figure 1. Kaplan Meyer survival curve for all-cause mortality according to atrial fibrillation during 12-year follow-up

Figure 1. Kaplan Meyer survival curve for all-cause mortality according to atrial fibrillation during 12-year follow-up

338x190mm (96 x 96 DPI)

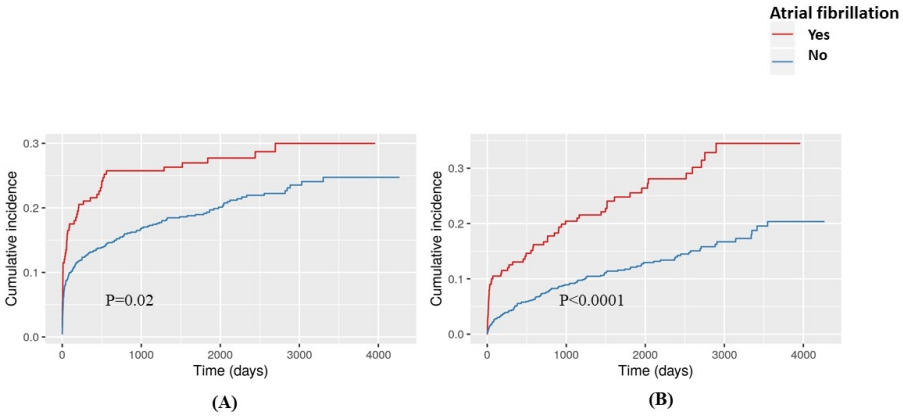


Figure 2. Cumulative incidence curves for stroke (A) and cardiovascular mortality (B) according to atrial fibrillation during 12-year follow-up

Figure 2. Cumulative incidence curves for stroke (A) and cardiovascular mortality (B) according to atrial fibrillation during 12-year follow-up

338x190mm (96 x 96 DPI)

The impact of atrial fibrillation and long-term oral anticoagulant use on all-cause and cardiovascular mortality: A 12-year evaluation of the prospective Brazilian Study of Stroke Mortality and Morbidity (EMMA)

Alessandra C Goulart[1,3], Rodrigo Diaz Olmos[1,3], Itamar S Santos[1,3], Gisela Tunes[2], Airlane P Alencar[2], Neil Thomas[5], Gregory Y. H. Lip[4,5], Paulo A Lotufo[1,3], Isabela M Benseñor[1,3]

[1] Center for Clinical and Epidemiological Research, Hospital Universitário, Universidade de São Paulo, Brazil

[2] Institute of Mathematics and Statistics, Universidade de São Paulo, Brazil

[3] School of Medicine, Universidade de São Paulo, Brazil

[4]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[5]Institute for Applied Health Research, University of Birmingham, Birmingham, UK

Corresponding author

Alessandra C. Goulart, MD, PhD

Center for Clinical and Epidemiological Research

Hospital Universitário

Av. Lineu Prestes 2565, Butantan – Cidade Universitária

CEP 05508-900 – São Paulo, SP - Brasil

E-mail: agoulart@hu.usp.br

Phone: 55-11-3091-9241; Fax: 55-11-30919241

Keywords: Stroke epidemiology, Stroke in developing countries and Stroke prevention.

Word count: 3,390

List of tables and figures:

Abstract

Background: Atrial fibrillation is a predictor of poor prognosis after stroke. **Aims**: To evaluate atrial fibrillation and all-cause and cardiovascular mortality in a stroke cohort with low socioeconomic status, taking into consideration oral anticoagulant use during 12-year follow-up. **Methods:** All-cause mortality was analyzed by Kaplan-Meier survival curve and Cox regression models to estimate hazard ratios and 95% confidence intervals (95% CI). For specific mortality causes, cumulative incidence functions were computed. A logit link function was used to calculate odds ratios (OR) with 95% CIs. Full models were adjusted by age, sex, oral anticoagulant use (as a time-dependent variable) and cardiovascular risk factors. **Results**: Of 1,121 ischemic stroke participants, 17.8 % had atrial fibrillation. Overall, 654 deaths (58.3%) were observed. Survival rate was lower (median days, interquartile range-IQR) among those with atrial fibrillation (531, IQR: 46-2,039) *vs*. non- atrial fibrillation (1,808, IQR: 334-3,301), p-log rank <0.0001). Over 12-year follow-up, previous atrial fibrillation was associated with increased mortality: all-cause (multivariable hazard ratios, 1.82; 95% CI: 1.43-2.31) and cardiovascular mortality (multivariable OR, 2.07; 95% CI: 1.36-3.14), but not stroke mortality. In the same multivariable models, oral anticoagulant use was inversely associated with all-cause mortality (oral anticoagulant time-dependent effect: multivariable hazard ratios, 0.47; 95%CI: 0.30-0.50, p=0.002) and stroke mortality (oral anticoagulant time-dependent effect ≥ 6 months: multivariable OR, 0.09; 95% CI: 0.01-0.65, p-value=0.02), but not cardiovascular mortality. **Conclusions**: Among individuals with low socioeconomic status, atrial fibrillation was an independent predictor of poor survival, increasing all-cause and cardiovascular mortality risk. Long-term oral anticoagulant use was associated with a markedly reduced risk of all-cause and stroke mortality.

Background

Despite the decrease in age-standardized cardiovascular disease (CVD) mortality rates, the burden of stroke is high, particularly in low-middle income countries.[1] Moreover, atrial fibrillation (AF) related stroke is associated with worse outcomes such as functional disability and higher mortality rates compared to stroke patients without AF.[2-6] Of note, AF is responsible for about 20% of ischemic strokes (IS), and this rate increases with age.[7] Regardless of potential confounders such as age and traditional cardiovascular risk factors, AF is considered an independent predictor of mortality in both sexes.[8]

Despite the increase in the AF prevalence and incidence, an improvement in the survival and stroke risk rates has been reported in a 50-years trend analysis performed in a large prospective cohort from a high-income country.[9] These findings may indicate that more awareness about the disease and effective treatment of AF might be associated with reduced stroke burden.[9] Indeed, the benefit of both oral anticoagulant (OAC) and non-vitamin K antagonist oral anticoagulants (NOAC) as primary prevention reducing stroke, systemic embolic events, and cardiovascular mortality with significantly reduced bleeding, has also been attested in previous clinical trials.[10] On the other hand, the cessation of OAC represents an independent predictor of stroke, cardiovascular adverse outcomes, and mortality.[11]

Oral anticoagulant therapy in AF related stroke has proved to prevent recurrent stroke and to reduce mortality, as well.[12,13] Despite this fact, the benefit of long-term OAC use after an AF-related stroke was previously verified only one study performed with a population from a high-income country.[12]

In low-middle income countries, including Brazil, the more difficult access to specialized medical treatment, rehabilitation services, and the lack of medication adherence impacts on the overall burden of stroke, particularly mortality.[14-16] Although there are initiatives to improve patient knowledge regarding AF and OAC therapy in high-income countries[17,18] almost nothing was done in low- and middle-income countries.

Aims

Thus, we aimed to evaluate the impact of AF on long-term all-cause and cardiovascular mortality, considering OAC use in a time effect analysis, in a low- socioeconomic status population attending a secondary community hospital in the city of São Paulo-Brazil.

Materials and Methods

Population and design study

Study subjects were participants in the Study of Stroke Mortality and Morbidity (EMMA study), a well-characterized, long-term stroke surveillance cohort that has been ongoing since 2006. The EMMA study was based on a Stepwise Approach to Stroke Surveillance (STEPS Stroke-World Health Organization).[19,20] Further information describing the study has been published elsewhere.[21] All patients older than 18 years-old with symptoms of acute stroke admitted to the Emergency Department of HU-USP (Hospital Universitário - University of Sao Paulo - Brazil) were invited to participate in the hospital phase of the EMMA study. The HU-USP is a secondary community hospital located in a low-income area with approximately 500,000 inhabitants, on the west side of São Paulo.

Written informed consent was obtained from all EMMA participants or from their advocate (usually a close family member). The study was approved by the Research Ethics Committee of the HU-USP, São Paulo, Brazil.

EMMA data collection

All data were collected by trained interviewers at hospital admission, at 1-month, 6-months, according to the World Health Organization (WHO) STEPS Manual.[19] As an extension of WHO STEPS stroke, we evaluated EMMA participants yearly or until death up to 12 years of follow-up from the baseline of the EMMA study. All losses prior to 12 years were censored at the last date on which they were contacted or when information about their vital status (alive) was confirmed by telephone contact or electronic hospital registers. Mortality data were confirmed by official death certificates in collaboration with the city of São Paulo's health statistics system (PRO-AIM, Program for Improvement of Mortality Information in the Municipality of São Paulo), State Health Offices (SEADE Foundation, São Paulo State Healthcare Data Analysis System) and the Brazilian Ministry of Health. All information gathered during the follow-up of the EMMA study is updated yearly.

Stroke definition

In the EMMA cohort, stroke was defined according to WHO criteria as "a focal (or at times global) neurological impairment of sudden onset, lasting more than 24 hours (or leading to death), and of presumed vascular origin.[19] Furthermore, stroke diagnosis was classified according to International Classification of Diseases, 10th Edition (ICD-10: I60-I63.9). Here, we analyzed only individuals with IS (I63.X).

Socio-demographic and Clinical data

Socio-demographic information (age, education, marital status and race as self-reported skin color: white, mixed, black and yellow), stroke characteristics (stroke subtype and recurrence), pre-existing cerebrovascular risk factors (CVRF) such as smoking, alcohol consumption and multi-morbidities such as hypertension, diabetes mellitus, dyslipidemia, heart failure, and coronary heart disease, chronic obstructive pulmonary disease , dementia and chronic kidney disease were evaluated at hospital admission. All information about clinical comorbidities (prior to index event) were self-reported and then validated by two senior medical researchers, based on medical registries during follow-up. The diagnosis of AF at baseline was based on at least one ECG record during the hospital admission or, alternatively, before the index event, if this information was present. If available, holter was also considered, but it was not an obligatory criterion for AF diagnosis in the EMMA cohort. Data on medication use such as anti-hypertensive, lipid-lowering, anti-diabetic, antiplatelet and OAC medications were collected at hospital admission (study baseline), after hospital discharge and during follow-up (at 6 months and yearly). Degree of functional disability status was evaluated by modified Rankin Scale (mRS) at 1 month and 6 months after the stroke. Impairment of functionality was categorized from 0 to 2 (mild or independent), from 3 to 5 points (moderate-severe or dependent) and 6 points corresponded to death after stroke.

Statistical analysis

Categorical variables were analyzed by the Chi-square test and presented as absolute and relative frequencies. As continuous variables had non-parametric distribution, they were analyzed by Kruskal-Wallis test and presented as median values with respective

interquartile range (IQR). Sociodemographic and clinical variables were analyzed according to AF status at study baseline. The long-term mortality risk was also evaluated according to AF presence (reference group: No AF).

For all-cause mortality, Kaplan-Meier survival curves were computed and Cox models were fitted to calculate hazard ratios (HR) with respective 95% confidence intervals (CI).[22,23] We added OAC use as a time-dependent covariate in the Cox models.

For specific causes of mortality such as stroke (ischemic and hemorrhagic) and CVD, cumulative incidence functions were computed by the Fine and Gray model in which the competing risk of death is considered.[24] For multiple regression analyses, the pseudo-values approach was used, and, a grid of time points was chosen.[25-27] Since OAC use status may have changed at 180 days, we chose time points after 180 days (specifically, 360, 540, 720, 1080, 1440, 2160, 2880 and 3600 days). We then added OAC use as a time-dependent covariate in pseudo-values models as follows: (1) in the first six months after the index event; and (2) six months after the index event and beyond. A logit link function was used to compute ORs with respective 95% CI.

All survival and cumulative incidence curves are presented using the observed values in the cohort, without adjustments. Regression models for all-cause, stroke and CVD mortality are presented as crude (Model 1), age and sex-adjusted (Model 2), further adjusted by oral anticoagulant therapy as time-dependent variable (Model 3) and as a full model further adjusted by hypertension, heart failure and CHD (Model 4).

Additionally, a stratified sensitivity analysis restricted to AF cases was performed to test the effect of OAC use in the first six months post stroke and six months after that.

For all analyses, p-values less than 0.05 were also considered as significant. Statistical analyses were performed with the statistical software SPSS version 26.0 and R.

Results

Baseline

Between April 2006 and September 2014, a total of 1,863 participant admitted in the Emergency Department of the Hospital Universitário from the University of São Paulo with suspected acute stroke were included in the EMMA study. Of them, we first identified 1,183 ischemic strokes (I63.X), 195 hemorrhagic strokes (I61.X), 36 unspecific strokes (I64), 161 stroke sequalae's (I69.X), 128 transitory ischemic attack (AIT, G45.X), 18 subarachnoid hemorrhage (I60), 46 (I67.X) with other cerebrovascular diseases, 94 with other non-neurological diagnoses such as hypoglycemic crisis and two had missing information on clinical data or imaging to confirm or exclude a stroke diagnosis. For the present study, we considered just the IS cases. Of 1,183 IS, we excluded 62 participants with missing information on AF diagnosis by ECG (5.2%) resting a sample of 1,121 participants (94.8% IS) over 18 years-old who had their confirmed stroke status and valid 12-lead ECG at baseline.

The main characteristics of the cohort are shown in Table 1. Among 1,121 individuals with IS (median age 70 years, IQR :59-79 y-old), 17.8% had AF at baseline and of these, only 10.5% underwent OAC therapy before the index event (Supplemental table 1). Compared with no AF participants, those with AF were seven years older (median age: 76, IQR :66-84 y-old versus 69 years, IQR :58-78 y-old; p<0.0001), most were female (57%) and had more associated comorbidities such as hypertension, CHD or heart failure. The proportion of IS patients with AF with more than two comorbidities was higher than non-AF IS patients (90.5% vs. 81.7%, p=0.002). Despite small clinical significance and

an equal median length of hospital stay (3 days), IS patients with AF required longer hospital stay than those with no AF (IQR: 2-9 vs. 2-7 days, p=0.03).

Moreover, the median value of CHA_2DS_2-VASC for those with AF diagnosis at baseline was 4 (interquartile range-IQR: 3-5).

Follow-up

At six months, although the absolute number of individuals with AF on OAC was low, we observed a slightly increase in the use OACs from 10.5% (pre-stroke) to 16.5% (6 months post-stroke). Regarding antiplatelet therapy use, we noticed a not a statistically significant difference between AF and non-AF groups at baseline (30% vs 24.7%, p=0.12). Post-hospital discharge, however, we observed a lower frequency of antiplatelets use among AF compared to non-AF patients (32.2% vs. 46.5%, p<0.0001) (Supplemental table 1). During follow-up, there was an increase in prevalence of OAC therapy after six months post-stroke (21.2%). (Table 2).

Of note, all participants under anticoagulation therapy were using Vitamin K antagonists (VKAs) except one which was using DOAC during the study follow-up.

No statistically significant differences were noticed between AF and no AF participants regarding recurrence of stroke, rehabilitation, number of hospitalizations or newly diagnosed comorbidities after hospital discharge (Table 2).

Overall, participants had a low reduction in their functional disability (mRS 3-5 points) from one to six months after the index event (33.2% and 26.4%, respectively) with similar proportions of recovering among AF (from 29% to 8.3%) and non-AF patients (from 34.1% to 13.8%). Also, the frequency of rehabilitation access during follow-up was also low (40.7%) regardless AF diagnosis at baseline. (Table 2). However, there were

more deaths among AF patients than non-AF patients at 1-month (31.0% vs. 17.0%, p=0.001) and 6-months (62.4% vs. 49.1%, p=0.01), respectively.

Among 200 AF related stroke cases, we noticed that only age influenced the use of OAC in the first six months. AF patients who were not under OAC was three years older than those who were on OAC therapy (median age: 70 y-old vs. 67 y-old, p=0.001, respectively). Other sociodemographic factors such as gender, race, educational level and marital status were not associated with the OAC use among stroke patients with AF. Finally, the CHA_2DS_2-VASC median score was higher among AF participants under OAC therapy (5, IQR: 3-5) than those with AF not anticoagulated (3, IQR: 2-4) during the follow-up.

Survival and mortality rates

In the EMMA study, more than half of the participants died (654 deaths/1,121, 58.3%) up to a 12-year follow-up. Particularly, the survival rate among patients with AF was lower than that verified in those without AF (median survival: 531 days (IQR: 46 to 2,039) vs. 1,808 days (IQR: 334 to 3,301), respectively, p-log rank<0.0001 (Figure 1). Moreover, higher mortality rates due to stroke and CVD were verified in AF patients compared to non-AF patients in these crude (non-adjusted) estimates (Figure 2).

In the multivariable regression models, previous AF (at baseline) was associated with almost two-fold risk of dying due to all-cause and CVD, as well. AF was a risk factor for death due to stroke in the crude model, but lost statistical significance after multivariable adjustments (Tables 3 and 4).

Regarding the OAC time-dependent effect considering the same multivariable models adjusted for age, sex, anticoagulant therapy time-dependent variable, hypertension, heart

failure, and CHD; we observed an inverse association between OAC use and all-cause mortality (multivariable HR, 0.47; 95%CI 0.30-0.50, p=0.002).

For specific causes of death, we also verified that OAC for 6 months or longer was associated with much lower stroke mortality odds (multivariate OR, 0.09; 95%CI 0.01-0.65, p-value=0.02). For cardiovascular mortality, no outcomes were significantly associated with OAC use.

Restricting our analyses to the 200 participants with AF, we also kept observing an inverse association between OAC use for 6 months or longer and both all-cause (multivariable HR, 0.38; 95%CI 0.19-0.75, p=0.005) and stroke (multivariable OR, 0.04; 95% CI, 0.004-0.55, p=0.01) in the models adjusted for age, sex, hypertension, heart failure and CHD as well.

Discussion

In this report from the EMMA cohort, we observed poor survival rates related to high cardiovascular mortality, over 12-years of follow-up among IS participants with AF. Despite anticoagulant use was associated with a time-dependent reduction in mortality outcomes, particularly stroke mortality rates in AF participants, most AF related stroke with high CHA2DS2-VASC score at baseline was not under OAC therapy during the follow-up.

We emphasize that the study population in the EMMA cohort comes from a low-income area in the city of São Paulo, Brazil, in which the burden of stroke is still high and health resources are limited and not sufficient to treat and monitor a population at high risk for cerebrovascular disease. In this context, our cohort is the first to show the prognostic value of AF and the effect of stroke secondary prevention with OAC on long-term survival in Latin America.

AF related stroke outcomes and anticoagulation

Despite difference on methodology or sociodemographic characteristics, we found the same pattern of higher risk for cerebrovascular events in patients with AF compared to those without AF in the EMMA study as in cohorts from high income countries.[2-5] Variations in the frequency of AF (13.6 to 29.45%) was mainly driven by different age-strata across studies.[2-5] Similar to EMMA study, higher mortality rates were also verified among AF related stroke compared to stroke patients without AF in other stroke cohorts. [2-5] Besides increased long-term mortality risk of AF, impacted on post-stroke disability compared to non-AF participants, as previously reported by other authors.[5]

Overall, the rates of anticoagulation from the baseline and during the follow-up in the EMMA cohort were lower than those previously verified in most cohorts performed in high-income countries.[2-4] Despite the importance of approaching anticoagulation after a stroke event associated to AF, few studies, particularly in high-income countries, have evaluated mortality risk considering OAC therapy in a longer follow-up[12] , as we did. A Swedish prospective cohort, the Lund Stroke Register, reported that after 10 years of follow-up, AF was independently associated with higher risk of all-cause mortality, especially for those with permanent AF without OAC (HR 2.28; 95%CI: 1.38–3.77, p = 0.001). However, neither specific causes of death nor time-dependent effect of OAC use were evaluated in this cohort. [12]

We found a time-dependent inverse association between long-term OAC use and mortality, particularly related to stroke mortality. In addition to a known protective effect of OAC in the occurrence of new thromboembolic events in stroke patients with AF, non-use of OAC is also a marker of high mortality risk during follow-up. In fact, we found a high percentage of AF-related stroke who had a CHA_2DS_2-VASC ≥ 2 at baseline (94%),

but most of them was not under OAC neither before the index event (89.5%) nor during the follow -up (83.5% within the first six months and 78.8% longer than six months after stroke). As previously described in the literature, the underuse of OAC in individuals who would primarily benefit from this medication may occur for many reasons. [11, 28-30] Besides formal contraindications for the OAC therapy, it has been reported advanced age with higher risk of bleeding, more severe comorbidities with low predicted overall survival, low patient´s compliance, insufficient structure in the public health facilities to perform regular international normalized ratio monitoring, doctor´s concern about the low patient´s comprehension of AF and the risk of complications as bleeding as important barriers to the use of OAC , including for the secondary prevention of stroke.[11, 28-30]

In the public health context, it is important to know the inter-regional differences to better understand the occurrence of chronic and disabling conditions. The EMMA dataset provides information regarding the prognostic value of AF, considering OAC therapy, in a low-income population affected by stroke. In this subset of participants from EMMA study, we found just one participant under NOAC. Although NOACs are available in Brazil for more than a decade, as previously reported by other authors[31], its use is low or almost inexistent among people with low-socioeconomic status because, unlike warfarin, there is no free availability of NOACs in Brazilian primary care units. A recent primary care-based cross-sectional study (2009-2016) reaffirmed our data. It was reported a low use (14.8%) of OACs even among those at high-risk of stroke and, no NOACs use was observed for stroke prevention among low-income population evaluated in this study.[31] Although we don't have specific information about medical visits and medication adherence after a stroke event, we could hypothesize that low socioeconomic patients affected by stroke have insufficient access to secondary stroke prevention. This is further supported by our finding of a low proportion of patients under rehabilitation after stroke.

Strengths

Particularly in Brazil, which has one of the highest rates of cerebrovascular disease in Latin America[20,32], these findings from the EMMA study corroborate for the understanding of the burden of AF, including the underuse of OAC therapy. In this report, we provide unique data on long-term mortality, which until now was lacking in low-middle income countries. Our study population was a well-characterized stroke cohort marked by high rates of cerebrovascular risk factors and lower survival rates, particularly in those participants with AF who were not on OAC therapy six months after an acute event.

The present study has a robust validation process of the stroke cases, including the collection of data on all cerebrovascular risk factors such as AF status and medication (prior to and during follow-up after an index event), entirely supervised by the medical research team. Regarding statistical methodology, we applied competitive risk analyses to evaluate specific causes of mortality that were not previously demonstrated by other studies in this field.

Limitations

Our study has some limitations. In spite of the fact that we did not find any AF after the index event, we cannot rule the possibility of paroxysmal AF during the follow-up of the study. The EMMA cohort is based on data from a secondary community hospital, in which it is not offered specialized treatment (thrombolysis/thrombectomy). Regularly, all IS cases who have an indication of any acute therapies are transferred to a tertiary hospital. In this subsample from the EMMA study, however, we did not have any case who received thrombolysis during acute phase, mainly due to exceeded time for acute stroke therapies considering the interval between stroke onset symptoms and hospital

admission. We don't have full information about NIH stroke scale or another measure of disability at hospital admission for all participants included in the present study. Since this is an observational study, we cannot rule out the possibility of immortal time bias in our analyses.[33,34] However, our choices to consider OAC use as a time-dependent variable may have minimized the occurrence of this bias. [33,34] Finally, we did not distinguish between the clinical types of AF (valvular vs nonvalvular) or duration (paroxysmal, persistent and permanent AF) in our study, which might have implications for mortality risk after a stroke event, as previously described by other authors.[12]

Conclusions

In the EMMA cohort, AF is an independent predictor of poor survival, increasing all-cause and particularly CVD mortality risk. Long-term OAC use was associated with a reduced risk of stroke mortality among AF related stroke in a population with low socioeconomic status.

Acknowledgements

We are grateful to the researchers and physicians linked to the EMMA study, as well as collaborators from health statistics systems (PRO-AIM, Program for Improvement of Mortality Information in the Municipality of São Paulo), State health offices (SEADE Foundation, São Paulo State Healthcare Data Analysis System) and the Brazilian Ministry of Health.

Sources of funding:

This study was funded by the São Paulo Research Support Foundation of the State of São Paulo (FAPESP), under the Number # 2018/05512-3. The partial support of the NIHR Global Health Research Group on AF management is acknowledged.

Conflict of interest

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

Other authors: None to declare

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383:245-54.

2. Andrew N, Kilkenny M, Harris D, Price C, Cadilhac DA. Outcomes for people with atrial fibrillation in an Australian national audit of stroke care. Int J Stroke. 2014;9:270-77

3. Lamassa M, Di Carlo A, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke 2001; 32:392–98.

4. Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke 2005;36:1115–19.

5. Lin S, Wu B, Hao ZL, Kong FY, et al. Characteristics, treatment and outcome of ischemic stroke with atrial fibrillation in a Chinese hospital-based stroke study. Cerebrovasc Dis 2011;31:419–26.

6. Healey JS, Oldgren J, Ezekowitz M, et al. RE-LY Atrial Fibrillation Registry and Cohort Study Investigators. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet. 2016;388:1161-69.

7. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015; 131: e29–322.

8. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study. Circulation. 1998;98:946-52.

9. Schnabel RB, Yin X, Gona P, Larson MG, et al. 50 Year Trends in Atrial Fibrillation Prevalence, Incidence, Risk Factors, and Mortality in the Framingham Heart Study: A Cohort Study. Lancet. 2015;386:154-62.

10. Link MS, Giugliano RP, Ruff CT, et al. ENGAGE AF-TIMI 48 Investigators. Stroke and Mortality Risk in Patients with Various Patterns of Atrial Fibrillation: Results From the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48). Circ Arrhythm Electrophysiol. 2017;10 (1). pii: e004267.

11. Rivera-Caravaca JM, Roldán V, Esteve-Pastor MA, et al. Cessation of oral anticoagulation is an important risk factor for stroke and mortality in atrial fibrillation patients. Thromb Haemost. 2017;117:1448-54.

12. Baturova MA, Lindgren A, Carlson J, Shubik YV, Bertil Olsson S, Platonov PG. Non-permanent atrial fibrillation and oral anticoagulant therapy are related to survival during 10 years after first-ever ischemic stroke. Int J Cardiol. 2017; 1; 232:134-39.

13. Arnao V, Agnelli G, Paciaroni M. Direct Oral Anticoagulants in the Secondary Prevention of Stroke and Transient Ischemic Attack in Patients with Atrial Fibrillation. Intern Emerg Med. 2015;10:555-60.

14. Castro HHG, Alencar AP, Benseñor IM, Lotufo PA, Goulart AC. Multimorbidities Are Associated to Lower Survival in Ischaemic Stroke: Results from a Brazilian Stroke Cohort (EMMA Study). Cerebrovasc Dis. 2017;44:232-39.

15. Abreu FG, Goulart AC, Birck MG, Benseñor IM. Stroke at baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): a cross-sectional analysis. Sao Paulo Med J. 2018;136:398-406.

16. Chin YY, Sekinah H, Aryati A, Hassan BM. Prevalence, risk factors and secondary prevention of stroke recurrence in eight countries from south, east and southeast Asia: a scoping review. Med J Malaysia. 2018;73:90-9.

17. Smith DE, Xuereb CB, Pattison HM, Lip GY, Lane DA. TRial of an Educational intervention on patients' knowledge of Atrial fibrillation and anticoagulant therapy, INR control, and outcome of Treatment with warfarin (TREAT). BMC Cardiovasc Disord. 2010;10:21.

.

18. Heneghan CJ, Garcia-Alamino JM, Spencer EA, et al. Self-monitoring and self-management of oral anticoagulation. Cochrane Database Syst Rev. 2016 Jul ;7:CD003839.

19. World Health Organization. WHO STEPS stroke manual: the WHO STEPwise approach to stroke surveillance/noncommunicable diseases and mental health. World Health Organization; 2006. [cited 12/06/2010]. Available from: World Health Organization http://www.who.int/chp/steps/stroke/manual/en/index.html

20. Lotufo PA, Benseñor IM. Improving WHO STEPS Stroke in Brazil. Lancet Neurol. 2007;6:387-8.

21. Goulart AC, Bustos IR, Abe IM, et al. A stepwise approach to stroke surveillance in Brazil: the EMMA (Estudo de Mortalidade e Morbidade do Acidente Vascular Cerebral) study. Int J Stroke. 2010;5:284-9.

22. Kaplan EL, Meier P. Nonparametric Estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457–81.

23. Cox DR. Regression model and life tables. Series B (Methodological). J Royal Stat Soc. 1972; 34:187–220.

24. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. The Annals of Statistics 1988;16:1141-54.

25. Klein JP, Andersen PK. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. Biometrics. 2005;61:223-29.

26. Klein JP, Gerster M, Andersen PK, Tarima S, Perme MP. SAS and R functions to compute pseudo-values for censored data regression. Comput Methods Programs Biomed. 2008;89:289-300.

27. Graw F, Gerds TA, Schumacher M. On pseudo-values for regression analysis in competing risks models. Lifetime Data Anal. 2009;15:241-55.

28. Fornari LS, Calderaro D, Nassar IB, et al. Misuse of antithrombotic therapy in atrial fibrillation patients: frequent, pervasive and persistent. J Thromb Thrombolysis. 2007;23:65-71.

29. Clarkesmith DE, Lip GYH, Lane DA. Patients' experiences of atrial fibrillation and non-vitamin K antagonist oral anticoagulants (NOACs), and their educational needs: A qualitative study. Thromb Res. 2017;153:19-27.

30. Pritchett RV, Clarke JL, Jolly K, et al. Clinicians' views and experiences of prescribing oral anticoagulants for stroke prevention in atrial fibrillation: A qualitative meta-synthesis. PLoS One. 2020;15:e0232484

31. de Moraes ERFL, Cirenza C, Lopes RD, Carvalho AC, Guimaraes PO, Rodrigues AAE, de Paola AAV. Prevalence of atrial fibrillation and stroke risk assessment based on telemedicine screening tools in a primary healthcare setting. Eur J Intern Med 2019;67:36-41.

32. Brant LCC, Nascimento BR, Passos VMA, 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;20:116-28.

33. Suissa S. Immortal Time Bias in Pharmacoepidemiology. American Journal of Epidemiology. 2008;167: 492–99.

34. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in

Table 1. Baseline Characteristics of EMMA participants according to atrial fibrillation at baseline

	AF n= 200	No AF n= 921	Total N=1,121	P-value
Sociodemographic Characteristics				
Median age, years (IQR)	76 (66-84)	69 (58-78)	70 (59-79)	<0.0001
Male sex, %	86 (43.0)	514 (55.8)	600 (53.5)	0.001
Race (skin color), %				0.02
White	145 (72.5)	566 (61.7)	711 (63.7)	
Mixed	47 (23.5)	268 (29.2)	315 (28.2)	
Black	6 (3.0)	68 (7.4)	74 (6.6)	
Yellow	2 (1.0)	16 (1.7)	18 (1.6)	
Educational level, %				0.08
Illiterate	48 (24.1)	167 (18.1)	215 (19.2)	
1-7 years	96 (48.0)	437 (47.4)	533 (47.5)	
≥ 8 years	56 (28.0)	317 (34.4)	373 (33.3)	
Previous clinical comorbidities, %				
Two or more chronic comorbidities	181 (90.5)	752 (81.7)	933 (83.2)	0.002
Hypertension,	193 (96.5)	846 (91.9)	1,039 (92.7)	0.02
Dyslipidemia	96 (48.0)	500 (54.3)	596 (53.2)	0.11
Diabetes	114 (57.0)	518 (56.2)	632 (56.4)	0.85
Coronary heart disease	57 (28.5)	198 (21.5)	255 (22.8)	0.03
Heart failure	83 (41.5)	224 (24.3)	307(27.4)	< 0.0001
COPD	11 (5.5)	39 (4.2)	50 (4.5)	0.43
Chronic kidney disease	57 (28.5)	220 (23.9)	277 (24.7)	0.17
Dementia	12 (6.0)	29 (3.1)	41 (3.7)	0.052
Abusive alcohol consumption, %	27 (13.5)	173 (18.8)	200 (17.8)	0.08
Smoking, %				0.36
never	122 (61.0)	514 (55.8)	636 (56.7)	
current	59 (29.5)	296 (32.1)	355 (31.7)	
past	19 (9.5)	111 (12.1)	130 (11.6)	
First-ever stroke, %	140 (70.0)	615 (66.8)	755 (67.4)	0.38
Elapsed time since onset stroke symptoms, %				
< 24 hours	172 (86.0)	724 (78.6)	896 (79.9)	0.02
≥ 24 hours	28 (14.0)	197 (21.4)	225 (20.1)	
Length of Hospital stay, days (IQR)	3 (2-9)	3 (2-7)	3 (2-7)	0.03

cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010 Mar 12;340:b5087.

IQR: Interquartile range P-value derived from the Mann-Whitney test for continuous variables and Chi-square test for categorical variables
AF, atrial fibrillation
COPD, chronic obstructive pulmonary disease

Table 2. Clinical conditions after hospital discharge due to stroke (index event) in EMMA cohort according to the presence of atrial fibrillation at baseline

	AF n= 200	**No AF** n= 921	**Total** N=1,121	**P-value**
Recurrence of stroke, %	19 (10.7)	121 (13.8)	140 (13.3)	0.27
Modified Rankin scale, %				
At 1 month				
Functional independence (0-2 points)	58 (40.0)	314 (48.9)	372 (47.3)	0.001
Functional dependence (3-5 points)	42 (29.0)	219 (34.1)	261 (33.2)	
Deaths (6 points)	45 (31.0)	109 (17.0)	154 (19.6)	
At 6 months				0.01
Functional independence (0-2 points)	46 (29.3)	264 (37.1)	310 (35.7)	
Functional dependence (3-5 points)	13 (8.3)	98 (13.8)	111 (26.4)	
Deaths (6 points)	98 (62.4)	349 (49.1)	447 (51.5)	
Access to Rehabilitation, %	74 (44.0)	342 (40.1)	416 (40.7)	0.34
Number of hospitalizations				0.65
None	159 (89.8)	788 (89.9)	947 (89.8)	
One	16 (9.0)	71 (8.1)	87 (8.3)	
Two	1 (0.6)	15 (1.7)	16 (1.5)	
≥ Three	1 (0.6)	3 (0.3)	4 (0.4)	
Number of newly diagnosed comorbidities after stroke, %				0.62
None	163 (92.1)	789 (90.0)	952 (90.3)	
One	10 (5.6)	68 (7.8)	78 (7.4)	
≥ Two	4 (2.3)	20 (2.3)	24 (2.3)	
Oral anticoagulant therapy after stroke				
First six months, %				< 0.0001
Yes	33 (16.5)	57 (6.2)	90 (8.0)	
No	167 (83.5)	863 (93.8)	1,030 (92.0)	
Six months or longer, %				< 0.0001
Yes	14 (21.2)	22 (5.7)	36 (7.9)	
No	52 (78.8)	366 (94.3)	418 (92.1)	

P-value derived from the Mann-Whitney test for continuous variables and Chi-square test for categorical variables

AF, atrial fibrillation

Rehabilitation at some point of follow-up: speech or physical therapy

Table 3. Cox regression analysis for all-cause mortality according the presence of atrial fibrillation at baseline in the EMMA cohort

	No AF	AF	p-values
	Hazard ratio (95%CI)	Hazard ratio (95%CI)	
Model 1	Reference (1.00)	1.72 (1.43-2.10)	<0.0001
Model 2	Reference (1.00)	1.46 (1.21-1.75)	<0.0001
Model 3	Reference (1.00)	1.89 (1.49-2.39)	<0.0001
Model 4	Reference (1.00)	1.82 (1.43-2.31)	<0.0001

95%CI: confidence interval
Model 1: Crude
Model 2: Age and sex adjusted
Model 3: Further adjusted by oral anticoagulant therapy time-dependent variable
Model 4: Further adjusted by hypertension, heart failure and CHD
AF: atrial fibrillation

Table 4. Competitive risk regression analyses for stroke and cardiovascular mortality causes according the presence of atrial fibrillation at baseline in the EMMA cohort

	No AF	AF	p-values
Stroke	Odds ratio (95%CI)	Odds ratio (95%CI)	
Model 1	Reference (1.00)	1.61 (1.22-2.29)	0.01
Model 2	Reference (1.00)	1.17 (0.79-1.74)	0.43
Model 3	Reference (1.00)	1.30 (0.86-1.95)	0.21
Model 4	Reference (1.00)	1.31 (0.86-2.00)	0.20
Cardiovascular			
Model 1	Reference (1.00)	2.54 (1.75-3.72)	<0.0001
Model 2	Reference (1.00)	2.39 (1.62-3.53)	<0.0001
Model 3	Reference (1.00)	2.40 (1.61-3.59)	<0.0001

Model 4	Reference (1.00)	2.07 (1.36-3.14)	0.001

95%CI: confidence interval
Model 1: Crude
Model 2: Age and sex adjusted
Model 3: Further adjusted by oral anticoagulant therapy time-dependent variable
Model 4: Further adjusted by hypertension, heart failure and CHD
AF: atrial fibrillation