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Cardiovascular medications and long-term mortality among stroke survivors in the Brazilian Study of Stroke Mortality and Morbidity (EMMA)

short title: Cardiovascular medications and mortality

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Abstract

Aim: To investigate the association between medication use and long-term all-cause mortality in a Brazilian stroke cohort. **Methods**: Both ischemic and hemorrhagic stroke were evaluated. Medication use was assessed as: never, only pre-stroke, only post-stroke, and continuous use. We evaluated anti-hypertensives, anti-diabetic, lipid-lowering drugs, anti-platelets, and anti-coagulants. Cox regression models were adjusted for sociodemographic and cardiovascular risk factors. **Results:** Among 1,173 incident stroke cases (median age: 68; 86.8% were ischemic, 70% first-ever stroke), medication use was low (Overall: 17.5% pre-stroke, 26.4% post-stroke and 40% were under continuous use). Anti-hypertensives and anti-platelets (aspirin) were the most often continuous cardiovascular medication used, 83.5% and 72%, respectively. While statins (39.7%) and anti-diabetics (31.3%) were the least used. Medication use (pre- post-stroke and continuous use) was associated with a reduction in all-cause mortality risk, particularly among those under continuous use (multivariable hazard ratio, 0.52; 95% CI, 0.46-0.66) compared to never users. Among ischemic stroke patients, this effect was similar (multivariable hazard ratio, 0.52; 95% CI, 0.40-0.68). No significant associations were evident among hemorrhagic stroke. **Conclusions:** The risk of all-cause mortality was reduced by 48% among those with ischemic stroke under continuous use of medications. Secondary prevention should be more emphasized in clinical practice.

Keywords: Stroke epidemiology, Mortality of stroke, Stroke secondary prevention and medication use.

Introduction

Stroke is one of the leading causes of morbidity and mortality worldwide. [1,2] The aging population process is one of the main contributors to the increased burden of stroke which is more impacting in low-middle income countries (LMICs).[1,2] Indeed, most risk factors for stroke can be managed through adequate cardiovascular prevention medication use such as anti-diabetics, anti-hypertensives, and lipid-lowering medications.[1,3]

For non-fatal outcomes, a combination of anti-thrombotic, statins, and anti-hypertensive drugs is associated with an improvement in post-stroke functionality and a reduction in the risk of recurrent stroke.[3-7] Despite the importance of secondary prevention, suboptimal use of cardiovascular medications after stroke is evident even in settings with good healthcare access [8], especially among low socioeconomic populations.

Cardiovascular medication use, such as statin use, is also associated with better survival after stroke among adults and elderly. [6,9,10] Combined therapy (anti-hypertensives, statins, and anti-platelet medication) is even more effective in reducing post-stroke mortality. [11]

Prior publications describing cardiovascular medication use and mortality have focused on pharmacotherapy in wealthier countries.[6,9-12] Information about cardiovascular medication use and mortality particularly in LMICs, in which secondary prevention is a serious issue faced by the public health system, is lacking. Therefore, in this ancillary study from the Study of Stroke Mortality and Morbidity (EMMA), we aimed to investigate the impact of cardiovascular

prevention drug therapies on long-term mortality among a low socioeconomic status population afflicted by stroke.

Materials and Methods

Study design and population

Study subjects are participants in the Study of Stroke Mortality and Morbidity (EMMA study), a well-characterized, long-term stroke surveillance cohort, ongoing since 2006. The EMMA study was based on a Stepwise Approach to Stroke Surveillance (STEPS Stroke-World Health Organization. [13,14] All patients older than 18 years (median age: 68) with symptoms of acute stroke admitted to one single-center, the Emergency Department (ED) of the HU-USP (University Hospital of the University of Sao Paulo, Brazil), were invited to participate in the hospital phase of the EMMA study. [15] The HU-USP is a secondary community hospital located in a low-income area of approximately 500,000 inhabitants, on the west side of São Paulo city. Of note, all potential candidates for reperfusion therapies are regularly transferred to our referral center and, thus, they were not included in these analyses. Further information about the EMMA study has been published elsewhere.[15]

Written informed consent was obtained from all EMMA participants or from their advocate (usually a close family member). The study was approved by the local Ethical Committee.

EMMA data collection

All data were collected by trained interviewers at hospital admission, at 1-month and 6-months, according to the World Health Organization (WHO) STEPS Manual.[13,14] 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

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. This clinical definition has, therefore, four components: (1) A neurological impairment or deficit, (2) Sudden onset, (3) Lasting more than 24 hours (or leading to death), and (4) Of presumed vascular origin" [13], and all of them should be presented for inclusion as a stroke case in the EMMA study. Furthermore, stroke diagnosis was classified according to the International Classification of Diseases, 10th Edition (ICD-10: I60-I63.9). Here, we analyzed individuals with the main subtypes of stroke: IS (I63.X) and HS (I61.X).

Socio-demographic, clinical and pharmacotherapy 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 co-morbidities such as hypertension, diabetes mellitus, dyslipidemia, heart failure, and coronary heart disease, atrial fibrillation (AF), chronic obstructive pulmonary

disease, dementia, and chronic kidney disease were evaluated at hospital admission and during the follow-up. All information about clinical co-morbidities (prior to index event) and cardiovascular medication were validated by two senior medical researchers, based on medical registries. We considered all clinical diagnoses based on medical history and/or use of medications. Diagnosis of AF at baseline was defined by ECG tracings (before or at hospital admission). Data on medication use such as anti-hypertensive, lipid-lowering, anti-diabetic, anti-platelet, and anti-coagulants were collected at hospital admission (study baseline), 1 month after hospital discharge due to the index event. The degree of functional disability status was evaluated by the 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 the Kruskal-Wallis test and presented as median values with respective interquartile range (IQR). Sociodemographic, clinical, and medication for clinical chronic conditions (anti-hypertensive, anti-diabetic, lipid-lowering medication, anti-platelet, and anti-coagulants) variables were analyzed according to cardiovascular medication use based on their previous clinical conditions such as hypertension, dyslipidemia, diabetes atrial fibrillation and coronary artery disease (never used: never used any medication pre- or post-stroke, pre-stroke: medication discontinued post-stroke, post-stroke: medication initiated post-stroke, continuous

use: medication used pre-and post-stroke). The long-term mortality risk up to 12 years of follow-up was also evaluated according to cardiovascular medication use.

For all-cause mortality up to 12 years of follow-up after an incident event, Kaplan-Meier survival curves were computed and Cox regression models were fitted to calculate hazard ratios (HR) with respective 95% confidence intervals (CI). [16,17] Regression models are presented as crude (Model 1), age and sex-adjusted (Model 2), further adjusted by education attainment, marital status, hypertension, diabetes, dyslipidemia, smoking, stroke subtype e recurrent stroke (at baseline) (Model 3). Additionally, stratified sensitivity analysis by stroke subtype was performed.

Statistical analyses were performed with the statistical software SPSS version 27.0, and for all analyses, p-values less than 0.05 were considered significant.

Results

Between April 2006 and September 2014, 1,863 participants admitted in the ED, and identified as suspected acute stroke were included in the EMMA study. Of these, we first identified 1,183 ischemic strokes (IS; I63.X), 196 hemorrhagic strokes (HS; I61.X), 36 unspecific strokes (I64), 160 stroke sequalae (I69.X), 128 transitory ischemic attack (TIA, G45.X), 17 subarachnoid hemorrhage (I60), 25 (I67.X) with other cerebrovascular diseases, 118 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. From 1,379 IS and HS, we excluded 40 participants with missing information on medication at baseline or at hospital discharge and 165 who died before the follow-up (1-month after stroke) to update medication for clinical chronic conditions. Thus, the final sample was composed by 1,173 participants, 1,018 with IS (86.8%) and 155 with HS (13.2%), who had full information about

medication use at baseline (before the stroke) and after hospital discharge (1-month after stroke).

Stroke pharmacotherapy

The main characteristics of the cohort according to the use of medications for clinical chronic conditions are shown in Table 1. Of 1,173 stroke participants (median age 68 years, 55.6 % male and 18.8% of illiterates), 86.8% were ischemic, and 70% had a first-ever stroke. Regarding medication use, we noticed an overall low use. The use of medication for chronic clinical conditions was: 17.5% pre-stroke, 26.4% post-stroke, and 40% under continuous use. No patients without main cardiovascular conditions (hypertension, heart failure, dyslipidemia, diabetes) used anti-hypertensive, anti-diabetic, lipid-lowering medications. Overall, patients who never used or discontinued cardiovascular medication after stroke were younger, widowed, had IS and the index event was not a first-time stroke. Also, those reporting never using cardiovascular medications had the lowest frequency of co-morbidities. The percentage of men taking continuous medication was slightly higher compared to women (52.2% vs. 47.8%, $p<0.0001$). White and married participants reported a higher frequency of continuous use of medications for chronic co-morbidities. While educational status did not modify the use of medications, there was lower medication use (19%) in illiterate individuals. Among clinical characteristics, the use of continuous medications was the greatest among individuals with ≥3 co-morbidities (68.1%). Once again, we observed higher frequencies of main cerebrovascular risk factors in the subgroup under continuous use of cardiovascular medication compared to other subgroups.

Detailed information about pharmacotherapy during the follow-up is described in Supplementary Table 1. Overall, cardiovascular medication use was low in the EMMA cohort. The most frequent medication class used in pre-stroke and continuous use groups were anti-

hypertensives followed by anti-platelets, lipid-lowering drugs, anti-diabetics, and finally anti-coagulants. From the baseline status (pre-stroke) to one month after stroke, we observed an increase in the use of aspirin (32.4% to 49.4%), statins (16.6% to 25.8%), and OAC (4.9% to 9.4%), but not anti-hypertensives and anti-diabetic medications.

Among those under continuous use, we observed 83.5%, 72%, 39.7%, 31.3%, 13.4% of the use of anti-hypertensive, aspirin, statin, anti-diabetics, and OAC (mainly VKAs). The exclusion of hemorrhagic stroke did not modify our findings. Of note, all who were taking OAC had an ischemic stroke. Even among those with AF-related stroke (n=155/1,1173, 13.2%), the use of OAC was extremely low pre- and post-stroke, 3.1% and 9.3%, respectively. The use of aspirin was also low in this subset (26.2% pre-stroke and 48.8% post-stroke).

The Figure 1 shows a progressively higher degree of functional independence (0-2 points in the modified Rankin scale, mRS) as well, lower proportions of deaths, were observed among patients across the subgroups of cardiovascular medication use, particularly six-month after stroke. Supplementary Table 2 shows the other clinical outcomes for stroke patients during follow-up. Post-stroke (156, 51.3%) and under continuous use of medication (216, 45.6%) had higher access to rehabilitation compared to never use (68, 39.3%) and pre-stroke (60, 30.6%) subgroups, $p<0.0001$.

Survival and mortality rates

The overall survival rate was 50.4% (591 survivors / 1,173 total sample), which corresponded to a median lifetime of 5.7 years. The number of deaths over the 12-year follow-up was 582. Figures 2 and 3 show survival rates (IS and HS) up to 12 years according to cardiovascular medication use. Ischemic stroke patients who used medications for chronic conditions (anti-hypertensive, lipid-lowering, anti-diabetic, anti-platelet, and anti-coagulants) post-stroke or were under continuous use had better survival rates than those who use only pre-

stroke medications or those who never used them (Overall p-Log-rank < 0.0001). These associations were not significant for HS (Overall p-Log rank=0.26).

Table 2 shows that overall, using medication at any time (pre- post-stroke and continuous use) was associated with lower all-cause mortality risk, particularly among those under continuous use (all-cause mortality HR, 0.52; 95% CI, 0.40-0.66) compared to never users. Among IS patients, this effect was similar (all-cause mortality HR 0.52, 95% CI 0.40-0.68). No significant associations were evident among HS patients. Additional adjustments for other comorbidities such as AF, CHD, HF did not change the directions and significance of our main findings.

Discussion

Despite high rates of cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia observed in the EMMA cohort, we observed a low use of medications for chronic clinical conditions, mainly cardiovascular risk factors. After an incident stroke, among those who used medications, anti-hypertensives (IECA) and anti-platelets (aspirin) were the most often taken (at least 70% after stroke). Among those with AF-related stroke, the use of OAC (mainly VKA) barely reached 10% one month after a stroke event. The long-term risk of dying was substantially lower for those who reported using medications for chronic clinical conditions at least up to 1-month after stroke compared to those who reported never using those drugs. Our most meaningful finding, it was a reduction of 48% in the risk of all-cause mortality among those afflicted IS under continuous use of medication. The higher frequency of medication use for cardiovascular risk factors among men can be at least partially explained by the higher frequency of comorbidities, except for atrial fibrillation which was more frequent in women than men. Is it turn, the highest frequency of continuous use of medications among married participants might be a confounder bias for the association between higher use of continuous

use and men since the majority of married participants in our sample were men. Meanwhile, the higher frequency of continuous use of medication among those self-reported as White could be associated with more access to health services and medications in the local public facilities, regardless of sex.

To our knowledge, this is the first report evaluating the use of multiple medications for main cerebrovascular risk factors and long-term mortality in a stroke cohort performed in a middle-income country, like Brazil. Based on the present data, we highlight the importance of taking actions to increase the use of cardiovascular medication and improve the accessibility of health care services after a stroke event, since we observed low use of multiple cardiovascular medications in a high-risk population.

Most studies analyzing medication use and mortality in a stroke secondary prevention scenario have focused on specific drug classes. For example, blood pressure (BP) control with anti-hypertensive drugs reduces drastically the risk of a second event or death.[18] Also, data from a recent systematic review involving 46 randomized clinical trials (10 anti-platelet agents, 6 combinations with aspirin, and 4 OACs) revealed anti-platelets improved ischemic stroke or transient ischemic attack outcomes.[19]

Previous analyses from the EMMA study also revealed an impressive reduction in long-term mortality rates among those with AF stroke under warfarin use longer than six months after the acute event.[20] Of note, the main barriers to effective anti-coagulation therapy in low-middle income countries such as Brazil are the still high cost of DOACs and the lack of sites to periodically perform INR control for those AF stroke cases, which impacts morbidity and mortality after a stroke event particularly in the low-income population [21] as the case of the participants from the EMMA cohort. Statins also provide beneficial effects for long-term

survival, as well as, functional outcome.[6] Randomized trials showed that statins reduce the risk of having a first or recurrent stroke[7] and long-term mortality. [22,23]

All the evidence mentioned above shows that cardiovascular medication use is crucial in preventing poor outcomes such as stroke recurrence and mortality. However, the long-term use of multiple medications is associated with a decrease in medication adherence.[4] In fact, most stroke survivors do not take all their medications.[24] A large Brazilian cohort study demonstrated an even higher frequency of none medication use for secondary prevention of stroke in a population with more access to health care services [8] compared to our current study (23.7% vs. 15.2%).

Strengths and limitations

The present study has a robust validation process of the stroke cases, which were classified as the main subtypes of stroke (ischemic and hemorrhagic), including a collection of data on all cerebrovascular risk factors and medications (prior to and during follow-up after an index event), entirely supervised by the medical research team.

This study has some limitations, most of them related to selection bias. The EMMA cohort is based on data from one single center, a secondary community hospital, without specialized treatment options (eg. thrombolysis/thrombectomy). Although IS cases who have an indication of any acute therapies are usually transferred to our reference (tertiary hospital), we cannot rule out a selection bias from a highly selected segment of stroke patients from the EMMA cohort that limits the external generalization of our data. We did not have full information about the NIH stroke scale or another measure of disability at hospital admission, as well as, information on stroke recurrence was lacking for all participants included in the present study. The small number of HS did not allow us to have sufficient power to analyze

cardiovascular medication use and mortality. Further, we did not have sufficient data about chronic medication after one month of stroke and even the reasons that treatments were never initiated or discontinued among stroke patients included in the EMMA study. A potential selection bias is a reason for discontinuing medication use, which could be a marker of disease severity or mortality. In the EMMA participants. In less than 10% of the EMMA cohort, we collected information about medication adherence through a brief questionnaire and, the main reasons for discontinuation were the oblivion of patients and lack of convenience in the schedule of the dosage proposed by the doctor.

Further, a small sample of HS cases was a limitation that did not allow us to explore more consistently the relationship between medication use and mortality among this subset of patients.

Since this is an observational study, we cannot rule out the possibility of immortal time bias in our analyses. [25,26]

Conclusions

In the EMMA cohort, cardiovascular medication use was low, however, the continuous use was associated with a significantly better long-term survival after stroke with a reduction in the mortality risk up to 48%, particularly for those with ischemic stroke under continuous use up to 1-month after acute stroke. The use of cardiovascular medication as secondary prevention should be more emphasized in clinical practice.

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Disclosure statement

KASS, ACV, RDO, CR, TEG, GNT, ISS, PAL, IMB and ACG: Declare no conflict of interest.

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Figure Legends

Fig. 1. Functional impairment by modified Rankin- scale according to cardiovascular medication use in the EMMA cohort

Fig. 2. Kaplan Meyer survival curve for all-cause mortality according to cardiovascular medication use in ischemic stroke during 12-year follow-up in the EMMA cohort

Fig. 3. Kaplan Meyer survival curve for all-cause mortality according to cardiovascular medication use in hemorrhagic stroke during 12-year follow-up in the EMMA cohort

Supplementary table titles

Table 1. Pharmacotherapy among participants from the EMMA study during the follow-up

Table 2. Clinical conditions after hospital discharge due to stroke (index event) according to cardiovascular medication use in the EMMA cohort