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Atrial Fibrillation as an Ischemic Stroke Clinical and Economic Burden Modifier: A 15-Year Nationwide Study

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ABSTRACT

Background: Atrial fibrillation (AF) is a major risk factor for ischemic stroke (IS). Patients with AF may undergo preventive therapy. Although the AF impact in the clinical burden of IS has been studied, information is lacking in Southern Europe and there are no studies about the impact in potential years of life lost. Moreover, no nationwide or long-term study analyzed the economic burden of IS stratified by AF. **Objective:** To study the impact of AF in the clinical and economic burden of IS. **Methods:** We conducted a retrospective study using nationwide administrative data for all public hospitalizations in mainland Portugal from 2000 to 2014. We considered IS hospitalizations stratified by the presence of AF as secondary diagnosis. **Results:** Of the total 275,173 IS hospitalizations, 22.6% reported AF. The total number of IS hospitalizations increased from 14,836 in 2000 to 19,561 in 2014 (32% increase), with an increase of 138% in the AF group (from 2,411 to 5,727). In-hospital mortality decreased from 13.6% to 11.5% and was consistently higher in the AF group (17.3% vs. 11.1%). Mean charges were also higher in the AF group (€2297 vs. €2191). Age-adjusted potential years of life lost rate was higher in the group without AF (39.6 vs. 7.5). **Conclusions:** AF-associated IS hospitalizations more than doubled in the studied 15-year period. Also, AF was responsible for higher in-hospital mortality and hospitalization charges. These facts highlight the need for early detection of AF and preventive treatment to limit IS occurrence, its associated burden, and poorer health outcomes.

Keywords: atrial fibrillation, burden of illness, economics, ischemic stroke.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 33.5 million people worldwide [1]. Its prevalence is expected to double by 2050 [2], partly because of population aging [1]. In Portugal, its prevalence is estimated as 2.5% among the population older than 40 years and 10.5% among octogenarians [3].

On top of increasing the risk of death [4], AF is associated with an increased risk of stroke [5], a leading cause of morbidity and mortality worldwide [6]. AF has been documented in a range of 15% to 38% of the patients suffering from an ischemic stroke (IS) [7–21].

Several studies demonstrated that AF-related IS cases had more severe functional deficits and increased complication rates, leading not only to higher mortality, but also longer hospital stays and increased nursing care [7,8,12,16,22–24]. Economically, this is translated into higher direct costs, even when adjusted for various confounding factors [8].

Even though several studies have analyzed costs for AF-related ischemic strokes, a lot of disparities are present in their methodologies, especially regarding cost calculation [25], resulting in unavoidable obstacles in making accurate comparisons. To our knowledge, only Sussman et al. (United States) [8], Wang et al. (United States) [26], and Ali et al. (United Kingdom) [27] reported the costs for IS stratified by AF. The two US studies used MarketScan claims data, whereas the UK study was based on data from only one hospital [27].

Thus, our main goal was to study the impact of AF in terms of the clinical and economic burden of IS during a long time period (15 years) in the mainland Portuguese hospital-based population. We aimed specifically to describe the impact of AF in IS premature deaths, potential years of life lost (PYLL), hospitalizations, and mortality trends; to summarize hospital charges; and to describe the most commonly associated comorbidities/risk factors stratified by the presence of AF.

Methods

We conducted a retrospective observational study using an administrative database, containing records from all hospitalizations in

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public hospitals in mainland Portugal. The data were provided by the Portuguese Ministry of Health's Central Administration for the Health System. Diagnoses were coded using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*).

We included all inpatient discharges with a principal diagnosis of acute IS (*ICD-9-CM* codes 433.x1 or 434.x1), between January 1, 2000, and December 31, 2014. We considered each hospitalization as an independent episode and included patients of all ages. Discharges with IS as a secondary diagnosis were not included in our analysis, and were rather studied in a subanalysis.

IS hospitalizations were divided into two groups: with AF (AF-IS) and without AF (non-AF-IS) as secondary diagnosis using *ICD-9-CM* code 427.3x (also includes atrial flutter), which might reflect either valvular or nonvalvular AF.

We studied patients' characteristics (sex and age) and hospitalization characteristics (admission dates, secondary diagnoses, discharge outcomes, discharge dates, and charges). In Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.018, we show the IS comorbidities/risk factors (based on secondary diagnoses coded in *ICD-9-CM*) as well as the presence of preventive therapy before hospitalization (i.e., long-term use of anticoagulants, antiplatelets, and aspirin—the latter two with the *ICD-9-CM* codes first introduced in 2006).

The annual IS hospitalization rate (i.e., hospitalizations per 100,000 person-years) was calculated by dividing the total number of IS hospitalizations by the sum of the annual mainland Portuguese population (data extracted from the National Statistics Institute [28]). Mortality rate (i.e., deaths per 100,000 person-years) was calculated by dividing the number of in-hospital deaths by the sum of the annual mainland Portuguese population. Both rates were standardized for age, according to the Scandinavian standard population—the most suitable for European populations [29]. Moreover, we calculated the in-hospital mortality rate (%) by dividing the total number of in-hospital deaths by the total number of hospitalizations, that is, the proportion of IS hospitalizations with death as patient discharge status.

We also considered in-hospital premature deaths (in-hospital deaths of patients 75 years old or younger) and PYLL, that is, the number of years lost because of death occurring earlier than a chosen reference age—75 years. We calculated the total PYLL, the mean PYLL (i.e., total PYLL divided by the number of deaths for those younger than 75 years), and the PYLL rate (i.e., the number of PYLL per 100,000 person-years) [30]. The overall differences between AF-IS and non-AF-IS were expressed as directly age-adjusted PYLL rates, according to the Scandinavian standard population [29,30]. Age-adjusted PYLL rates are a measure of premature mortality that gives greater emphasis on deaths at younger ages rather than those at older ages. It can be interpreted as the number of potential years of life that would be lost per 100,000 person-years of an actual population if it had the same age structure as that of the Scandinavian standard population [30].

We calculated charges in euros, according to the expenditure tables (reimbursement) for Portuguese National Health Service hospital costs, which were defined by governmental regulation in 2009 (in *Diário da República*) [31]. We considered expenditure tables from 2009 because they were the latest to consider the 3M™ All-Patient Diagnosis-Related Group (DRG) version 21, which was the only version available in our database for the entire studied period. This reimbursement is performed using the budget allocation model based on DRGs, which includes principal and secondary diagnoses, procedures, age, sex, and discharge destination [32]. We converted the calculated charges (in euros) to 2014 international dollars (I$) using the International Monetary Fund's conversion rate based on purchasing power parity for gross domestic product rate for the year of 2009 and the gross domestic product deflator index [33], by means of the CCEMG-EPPI-Centre cost converter v1.5 [34], so as to obtain an adequate cost comparison with studies from other countries. In fact, purchasing power parities are frequently used as measures of price competitiveness and as inputs into policy analysis requiring comparisons between countries [35]. Costs reported in several articles were also converted to 2014 international dollars, using the same methodology.

Pearson χ^2 tests were performed to compare comorbidities/risk factors, sex, in-hospital mortality, and premature in-hospital mortality between AF-IS and non-AF-IS. AF excess fractions were calculated by dividing the difference of relative frequencies of the comorbidities/risk factors between AF-IS and non-AF-IS by their AF-IS relative frequency (in percent), as presented in the following formula [36]:

$$\frac{f(\mathrm{AF}) - f(\mathrm{non-AF})}{f(\mathrm{AF})}.$$

The Mann-Whitney *U* test was used to compare age, charges and length of stay between the same groups. To assess trends in in-hospital mortality rate and charges, we used linear regression models, using "discharge year" as an independent variable. To adjust those trends for age, we included "age" as an independent variable.

All 95% confidence intervals were calculated either for rates, using the Byar method [37], or for proportions, using Wilson score [38,39]. We considered the significance level (*P* value) of 0.05. Descriptive, analytical, and inferential statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA).

Results

We identified 275,173 hospitalizations with a principal diagnosis of IS. Approximately 22.6% (n = 62,109; 95% confidence interval [CI] 22.4%–22.7%) had a diagnosis of AF, which increased from 16.3% (95% CI 15.7%–16.9%) in 2000 to 29.3% (95% CI 28.6%–29.9%) in 2014 (data not shown).

An overall IS hospitalization rate of 183.8 per 100,000 person-years (95% CI 183.3–184.7) and age-standardized hospitalization rate of 115.1 per 100,000 person-years (95% CI 114.5–115.5) were found. Hospitalization rate by age group (per 100,000 person-years) was 4.4 for 0 to 39 years, 41.5 for 40 to 49 years, 117.8 for 50 to 59 years, 297.2 for 60 to 69 years, 735.7 for 70 to 79 years, and 1452.6 for 80 years or older. Table 1 presents the number of IS hospitalizations and hospitalization rates by age group, sex, and AF.

The overall mean age at discharge was 74 ± 12 years, 79 ± 9 years in AF-IS and 72 ± 12 years in non-AF-IS ($P < 0.001$). Patients younger than 50 years represented 4.4% (n = 12,177) of the IS hospitalizations and only 3.0% (n = 368) of them had a diagnosis of AF.

Among all episodes of IS, 135,939 (49.4%; 95% CI 49.2%–49.6%) occured in male patients. Male sex was significantly more preponderant in non-AF-IS (n = 110,719 [52.0%]; 95% CI 51.8%–52.2%) than in AF-IS (n = 25,220 [40.6%]; 95% CI 40.2%–41.0%; $P < 0.001$).

Table 2 presents comorbidities/risk factors with relative frequency higher than 0.5%, comparing AF-IS and non-AF-IS. Overall, the most frequent comorbidities/risk factors were hypertension (63.9%), diabetes mellitus (27.0%), and dyslipidemia (25.3%). All but peripheral arterial disease had a statistically significant difference between both groups when considering *P* value from the Pearson χ^2 test (i.e., AF-IS and non-AF-IS). Those with a higher positive AF excess fraction were heart failure (+67.3%, from 6.0% to 18.3%), prosthetic cardiac valves (+66.0%, from 0.6% to 1.8%), valvular