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Oral Anticoagulation and the Incidence of Stroke Associated with Atrial Fibrillation in Mainland Portugal: A Modelling Study

Anticoagulação Oral e Incidência de Acidente Vascular Cerebral Associado a Fibrilhação Auricular em Portugal Continental: Um Estudo de Modelação

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ABSTRACT

Introduction: Atrial fibrillation is the most prevalent persistent dysrhythmia, contributing to a significant social and economic burden. The main objective of this study was to evaluate the association between oral anticoagulant use and the incidence of stroke associated with atrial fibrillation, in mainland Portugal.

Methods: The number of episodes of inpatient care with a main diagnosis of stroke and an additional diagnosis of atrial fibrillation, occurring monthly between January 2012 and December 2018, in individuals aged 18 years or over, was extracted from the hospital morbidity database. The number of patients with an atrial fibrillation code documented in this database was used as a proxy for the prevalence of known atrial fibrillation. The number of anticoagulated patients was estimated from total medicine sales of vitamin K antagonists and novel oral anticoagulants (apixaban, dabigatran, edoxaban and rivaroxaban) in mainland Portugal. Descriptive analyses were performed, and seasonal autoregressive integrated moving average (SARIMA) models were built using the R software.

Results: The mean number of episodes of stroke per month was 522 (± 57). The number of anticoagulated patients increased gradually from 68 943 to 180 389 per month. The decreasing trend in the number of episodes has been observed since 2016, along with the increased use of new oral anticoagulants compared to vitamin K antagonists. The final model indicated that the increase in oral anticoagulation use between 2012 and 2018, in mainland Portugal, was associated with a decrease in the number of episodes of stroke associated with atrial fibrillation. It was estimated that the shift in the type of anticoagulation used, between 2016 and 2018, was associated with a reduction of 833 episodes of stroke in patients with atrial fibrillation (4.2%).

Conclusion: The use of oral anticoagulation was associated with a reduced incidence of stroke in patients with atrial fibrillation in mainland Portugal. This reduction was more relevant in the period between 2016 and 2018, and is probably related with the introduction of the novel oral anticoagulants.
Keywords: Anticoagulants/therapeutic use; Atrial Fibrillation/complications; Portugal; Stroke/prevention & control

RESUMO

Introdução: A fibrilhação auricular é a disritmia persistente mais prevalente, tendo um importante impacto social e económico. O objetivo principal deste estudo foi avaliar a associação entre a utilização de anticoagulantes orais e a incidência de acidente vascular cerebral associado a fibrilhação auricular, em Portugal continental.

Métodos: A base de dados de morbilidade hospitalar foi utilizada para a contabilização dos episódios de internamento com um diagnóstico principal de acidente vascular cerebral e um diagnóstico adicional de fibrilhação auricular, ocorridos durante cada mês do período em análise (janeiro de 2012 a dezembro de 2018), em indivíduos com idade igual ou superior a 18 anos. O número de doentes com registo de fibrilhação auricular presentes nesta base de dados foi utilizado como um *proxy* da prevalência de fibrilhação auricular conhecida. O número de doentes anticoagulados foi estimado a partir das estatísticas das vendas de antagonistas da vitamina K e novos anticoagulantes orais (apixabano, dabigatrano, edoxabano e rivaroxabano) em Portugal continental. Foi realizada uma análise descritiva das variáveis, construindo-se depois modelos auto-regressivos integrados de médias móveis sazonais (*seasonal autoregressive integrated moving average*, SARIMA), com recurso ao *software R*.

Resultados: Ocorreram, em média, 522 (± 57) episódios de acidente vascular cerebral por mês. Verificou-se um aumento gradual do número de doentes anticoagulados, passando de 68 943 para 180 389, por mês. A tendência decrescente no número de episódios verificou-se a partir de 2016, a par da maior utilização dos novos anticoagulantes orais, comparativamente aos antagonistas da vitamina K. O modelo final estimado indicou que o aumento do consumo de anticoagulação oral entre 2012 e 2018 em Portugal continental foi associado a um decréscimo do número de acidentes vasculares cerebrais associados a fibrilhação auricular. Estimou-se que, entre 2016 e 2018, a mudança no tipo de anticoagulação se associou a uma redução de 833 episódios de acidentes vascular cerebrais em doentes com fibrilhação auricular (4,2%).

Conclusão: A anticoagulação oral associou-se à redução da incidência de acidente vascular cerebral em doentes com fibrilhação auricular, em Portugal continental. Esta redução foi mais relevante no período 2016 a 2018, em provável relação com a introdução dos novos anticoagulantes orais.
Palavras-chave: Acidente Vascular Cerebral/prevenção e controlo; Anticoagulantes/uso terapêutico; Fibrilhação Auricular/complicações; Portugal

INTRODUCTION

Atrial fibrillation (AF) represents the most prevalent persistent dysrhythmia in clinical practice,[1] with an important social and economic impact.[2]

Stroke is particularly relevant due to its morbidity and

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mortality; a five times higher estimated risk of stroke - a major cause of death in Portugal – has been found in patients with AF.[3,4]

Oral anticoagulation (OAC) therapy, which has been recommended for at least a decade to reduce the risk of stroke in the presence of AF, has seen its role strengthened by the introduction of the new oral anticoagulant (NOAC) drugs.[5] Currently, OAC drugs are recommended in the presence of a CHA_2DS_2-VASC score ≥ 1 in men and ≥ 2 in women, with an adequate haemorrhage risk profile.[1]

Approximately 73% of patients with AF and an indication for anticoagulation were on anticoagulation therapy in a recent study carried out in the Northern region of Portugal (2016 – 2018 data).[6] This is in contrast to the previous estimate of 57% found by the FATA study in 2015.[7]

Worldwide, several studies have sought to estimate the relationship between the increasing use of OAC drugs and the incidence of stroke, with heterogeneous results.[8,9] Some of the gaps found in previous studies were filled by the study by Cowan *et al.*, more recently, by including the known prevalence rate of AF (rather than the AF prevalence rate estimated by screening studies) and parameters related to the estimated use of OAC drugs by English patients presenting with AF.[10] A decrease in the stroke rate in AF patients associated with the use of OAC drugs (2011 – 2016) has been found in this study.[10]

The main objective of this study was the assessment of the impact of the use of oral anticoagulants on the incidence of AF-related stroke in mainland Portugal.

METHODS

The impact of the use of oral anticoagulants on the incidence of stroke affecting AF patients in mainland Portugal was assessed between January 2012 and December 2018.

A multidimensional strategy, using two real databases (real world data) was adopted, as the use of a single source did not allow the collection of the required information at an individual level; the following variables were considered: inpatient care episodes of stroke affecting AF patients, patients on anticoagulation and prevalence of AF.

Data were mainly obtained from (i) the hospital morbidity database, made available under a collaboration protocol between the Administration of Health Services (*Administração Central dos Serviços de Saúde, I.P.*), and the Centre for Evidence-Based Medicine Studies (*Centro de Estudos de Medicina Baseada na Evidência*) at the Faculty of Medicine of the University of Lisbon, and (ii) the sales statistics provided by HMR - Health Market Research.

No experimentation on animals or humans, nor any participants were involved. Clinical data irreversible anonymisation was ensured, as well as aggregate sales data, and any data cross-checking was prevented. The study followed the principles of the 2013 Helsinki declaration and therefore no request for a formal opinion from an ethics committee was required.

Inpatient care episodes of AF-related stroke

The hospital morbidity database (BDMH) was used to obtain relevant data on inpatient care episodes. The BDMH is an administrative record of inpatient care episodes and selected outpatient care episodes that occurred within the National Health Service (*Sistema Nacional de Saúde* - SNS) units.[11] Diagnoses and procedures coded from hospital files collected by coding doctors trained in the use of the International Classification of Diseases (ICD) were included.

The relevant cases for analysis were identified using the ICD-9, clinical modification (ICD-9-CM) for 2012 – 2016 and the ICD-10, clinical modification, and procedure classification system (ICD-10-CM/PCS) for 2016 – 2018 (the BDMH for 2016 showed around 96% of episodes coded according to ICD-9-CM and the remaining 4% according to ICD-10-CM/PCS). All inpatient care episodes that occurred during each month of the study timeframe, involving patients aged 18 and older, with a primary diagnosis of stroke (ischaemic or haemorrhagic) and an additional diagnosis of AF were considered. ICD-10-CM/PCS and ICD-9-CM codes used in the analysis are available in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19255/15144).

Patients on anticoagulation

In the absence of any available information on AF patients on anticoagulation or the ratio of AF patients on OAC drugs, the total number of patients on anticoagulation in mainland Portugal was considered, regardless of the therapeutic indication. The evolution in total sales of anticoagulant drugs (for any indication) was assumed that it was in line with that of anticoagulant drugs specifically used for stroke prevention in AF patients.

Data on the number of patients on anticoagulation within each month were estimated from sale statistics of vitamin K antagonists (VKA - acenocoumarol and warfarin) and NOACs (apixaban, dabigatran, edoxaban and rivaroxaban) in mainland Portugal, and were provided by Health Market Research (HMR). Obtaining the total number of milligrams sold within each month for each of the drugs considered (based on the characteristics of the packaging: dosage and number of tablets) was the first step. In a second step, the defined daily dose (DDD) was used to estimate the number of days of treatment, in addition to the number of patient-months on treatment.

Prevalence of AF

A 2.5% (95% CI: 2.2% - 2.8%) prevalence rate of AF was

estimated in Portugal by the FAMA study, affecting patients aged 40 and older.[12] However, only 1.6% in our group of patients were aware of the diagnosis. Since the publication of the FAMA study in 2010, other studies have described the impact on the prevalence of AF of the ageing population, as well as the use of additional screening methods.[7,13,14] To our knowledge, no longitudinal study characterising the evolution of the prevalence rate of AF in Portugal was ever published and, in particular, the prevalence rate of known (diagnosed) AF over the last decade. It is worth mentioning that the known prevalence rate of AF has a specific impact on the analysis, as a prior diagnosis of this arrhythmia is involved in the introduction of anticoagulation in patients with AF.

The BDMH was used to collect the required information. In this case, the number of patients aged 18 or older, who were coded with a diagnosis of AF (in any position) in at least one episode within each of the study years was estimated. The ICD-10-CM/PCS and ICD-9-CM codes used in the analysis are available in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19255/15144). The number of patients with an AF code in the BDMH was used as a proxy for the prevalence of known AF, reflecting not only the ageing of the population, but also the potential influence of other factors (greater diagnostic and recording capacity) within the study timeframe. It is worth mentioning that, in this case, the annual value of the parameter was assumed as valid for each of the months of that year, overriding the effect of the seasonality typical of the use of hospital care.

Statistical analysis

A linear regression model with (seasonal) ARIMA (autoregressive integrated moving average) errors was developed to describe the number of stroke episodes in AF patients at each time point *t*. This model allows the description of the number of stroke episodes as a function of the values recorded at other time points, such as those recorded during the preceding month or during the same month of the previous year. As a generalisation of ARIMA models, seasonal ARIMA models can be used for the modelling of series with a seasonal component, such as stroke episodes.

The descriptive analysis of the variables was initially carried out, using frequency tables and trend analyses of the time series obtained using the seasonal-trend decomposition using Loess (STL) method.

Different seasonal ARIMA models were built using the *auto.arima()* function of the forecast package,[15] using the R software (R Core Team 2019. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Different explanatory variables were used. In addition to those already described (patients on anticoagulation and AF patients registered in the BDMH), other time series were included (ratio of female AF patients, mean age of AF patients, severity of stroke episodes in AF patients, Charlson index of stroke episodes in AF patients), a categorical variable referring to the predominant type of anticoagulation (VKA *versus* NOACs), and an interaction term between this categorical variable and the series of the number of patients on anticoagulation.

The final model was selected using the corrected Akaike information criterion (AICc) as well as criteria related to predictive quality [root mean square error (RMSE), mean percentage error (RMPE) and mean absolute percentage error (MAPE)] and fit [adjusted coefficient of determination (R^2_a)]. The quality of the fit to data was assessed using the Ljung-Box test, based on the *checkresiduals* function of the forecast package.[15] The estimates of the sample autocorrelation (FAC) and partial autocorrelation (FACP) functions were also analysed.

RESULTS

Descriptive analysis

The number of stroke inpatient care episodes affecting patients diagnosed with AF ranging between 375 and 661 per month has been found, with an average of 522 (± 57) episodes and a median of 524 episodes (Fig. 1).

The analysis using the STL method showed that there was an increase in the number of stroke episodes in AF patients between January 2012 and November 2013, and again between July 2014 and July 2015, and between January and July 2016. These periods are interspersed with periods of decrease in the number of episodes. The downward trend remained unchanged from July 2016 until the end of the study timeframe (December 2018) (Fig. 2).

The number of cases was higher in the colder months (Fig. 3), suggesting a seasonal pattern, also found with the STL method.

The number of patients with AF recorded in the BDMH throughout each annual period was used in modelling the prevalence of known AF. There was an upward trend over the period analysed (Fig. 4A).

When the number of stroke episodes in patients with AF is standardised by the number of patients with AF records (by dividing the number of stroke episodes with AF diagnosis by the number of patients found in the BDMH each year), the initial upward trend in some periods disappears, leading to an overall downward trend (Fig. 4B).

There was a progressive increase in the number of patients on anticoagulation between January 2012 and December 2018 (Fig. 5A), ranging from a minimum of 68,943 to 180,389 patients per month, due to the rise in NOAC consumption (Fig. 5B), mainly between 2014 and 2015.

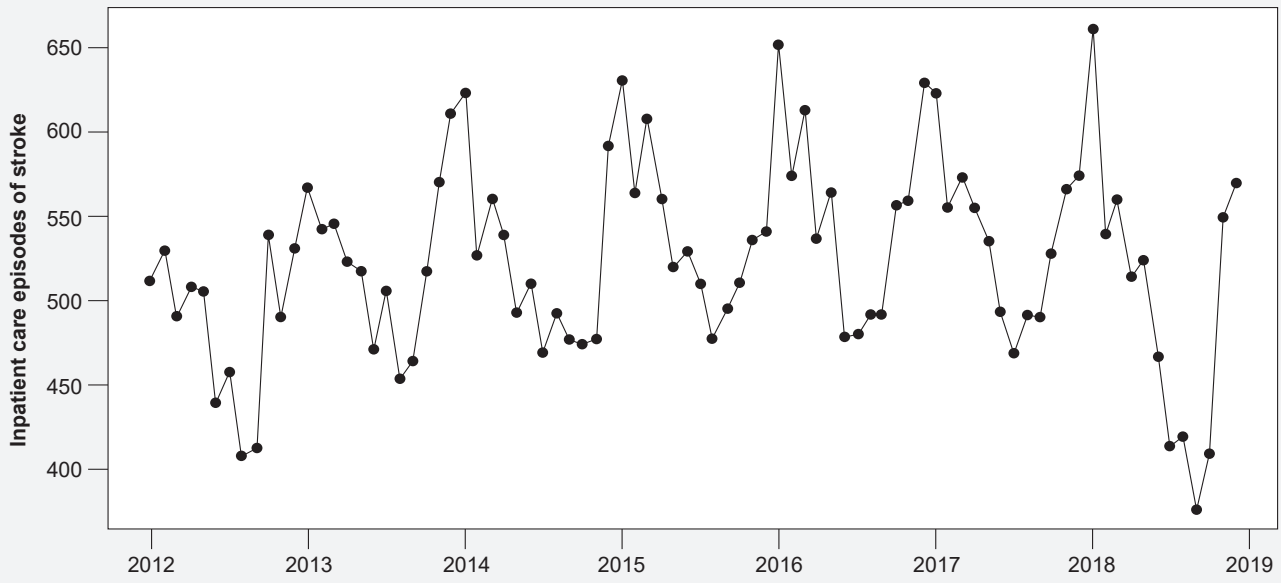

Figure 1 – Chronogram of the series of inpatient care episodes of stroke involving patients with AF in mainland Portugal between Jan 2012 and Dec 2018
Source: figure obtained by the authors based on the BMDH 2012-2018 data

A downward trend in the number of stroke episodes in AF patients has been found from 2016 onwards (as shown in Figures 2 and 5B), in addition to a change in the composition of the series referring to OACs (the number of patients on anticoagulation with NOACs outweigh the number of patients on anticoagulation with vitamin K antagonists) at the beginning of the same year. This has explained the inclusion of a categorical variable (taking a value of 1 for observations in 2016, 2017 and 2018) and the addition of this categorical variable in interaction with the series of the

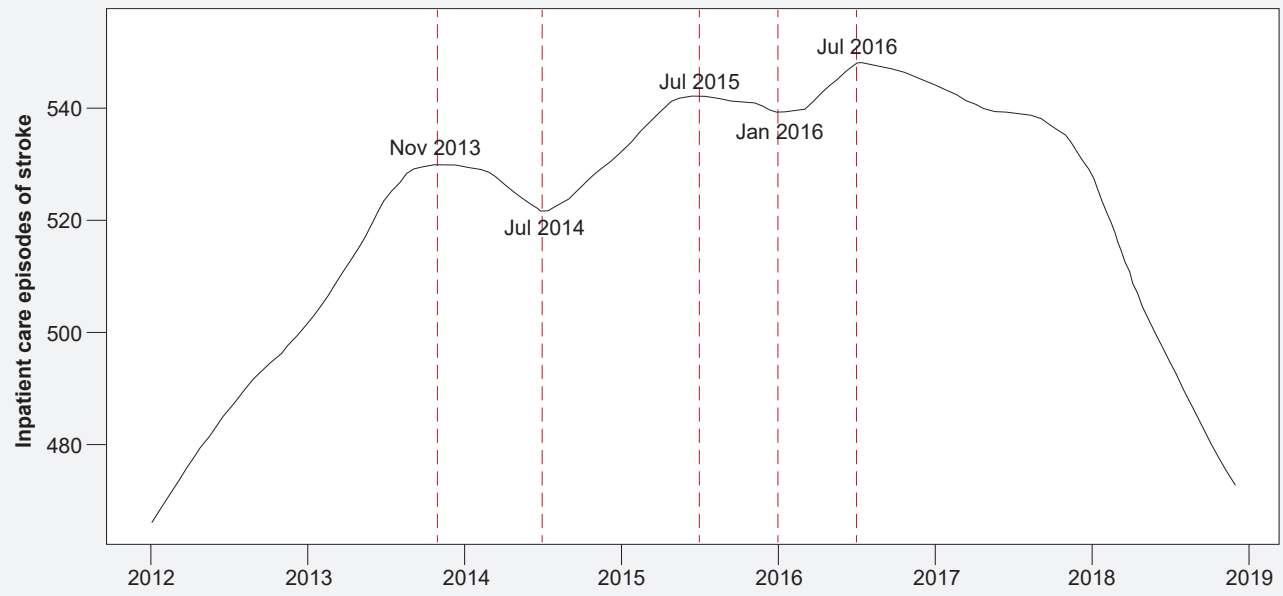

Figure 2 – Trend of the series of the number of inpatient care episodes of stroke involving patients with AF in mainland Portugal, from Jan 2012 to Dec 2018, obtained by the STL method
Source: figure obtained by the authors based on the BMDH 2012-2018 data

number of patients on anticoagulation.

Modelling of the number of stroke episodes in AF patients using a seasonal ARIMA model

Three explanatory series were used by the model with the best fit to data for explaining the evolution of the logarithm of stroke episodes ($E_{stroke,t}$) (according to the lowest AICc, EPM and EPAM values and the highest R^2_a value): (i) the logarithm of the number of patients treated with OAC ($\{X_{1,t}\}$), (ii) the interaction term between the categorical variable (with a value of 1 for the observations in 2016, 2017 and 2018) and the logarithm of the number of patients treated with OAC ($\{X_{2,t}\}$) and (iii) the number of patients with AF coding ($\{X_{3,t}\}$). The *p*-value of the Ljung-Box test (0.6549) confirms the suitability of the model for representing the time series under analysis, as well as analysing the sample FAC and FACP. The model equation is given by $E_{stroke,t} = -0.1376\, X_{1,t} - 0.0036\, X_{2,t} + 1.2137\, X_{3,t} + N_{t-12} + e_t - 0.5169\, _{et-12}$.

The chronogram of the series to be modelled (black) and the model selected to fit the data (magenta) are shown in Fig. 6, with a 95% confidence interval, shown in blue dashed lines.

The final estimated model showed that the increase in OAC consumption between 2012 and 2018 in mainland Portugal was associated with a decrease in the number of AF-related strokes. The results can be interpreted as follows: an 1% increase in the number of patients on anticoagulation between January 2012 and December 2015 (categorical variable = 0) was expected to lead to a 0.1376% decrease in the number of stroke episodes in AF patients. On the other hand, an 1% increase in the number of patients on anticoagulation between January 2016 and December 2018 (categorical variable = 1) was expected to lead to a 0.1413% decrease in the number of stroke episodes in AF patients. In addition, even though this was the model that was selected, all the models identified and analysed pointed in the same direction, i.e., therapy with oral anticoagulants is associated with a reduction in the number of stroke episodes associated with AF.

This model also allowed the assessment of a counterfactual scenario for 2016-2018, removing the effect on the response variable due to the OAC shift within this period (included through the interaction term between the categorical variable and the number of patients on anticoagulation). In

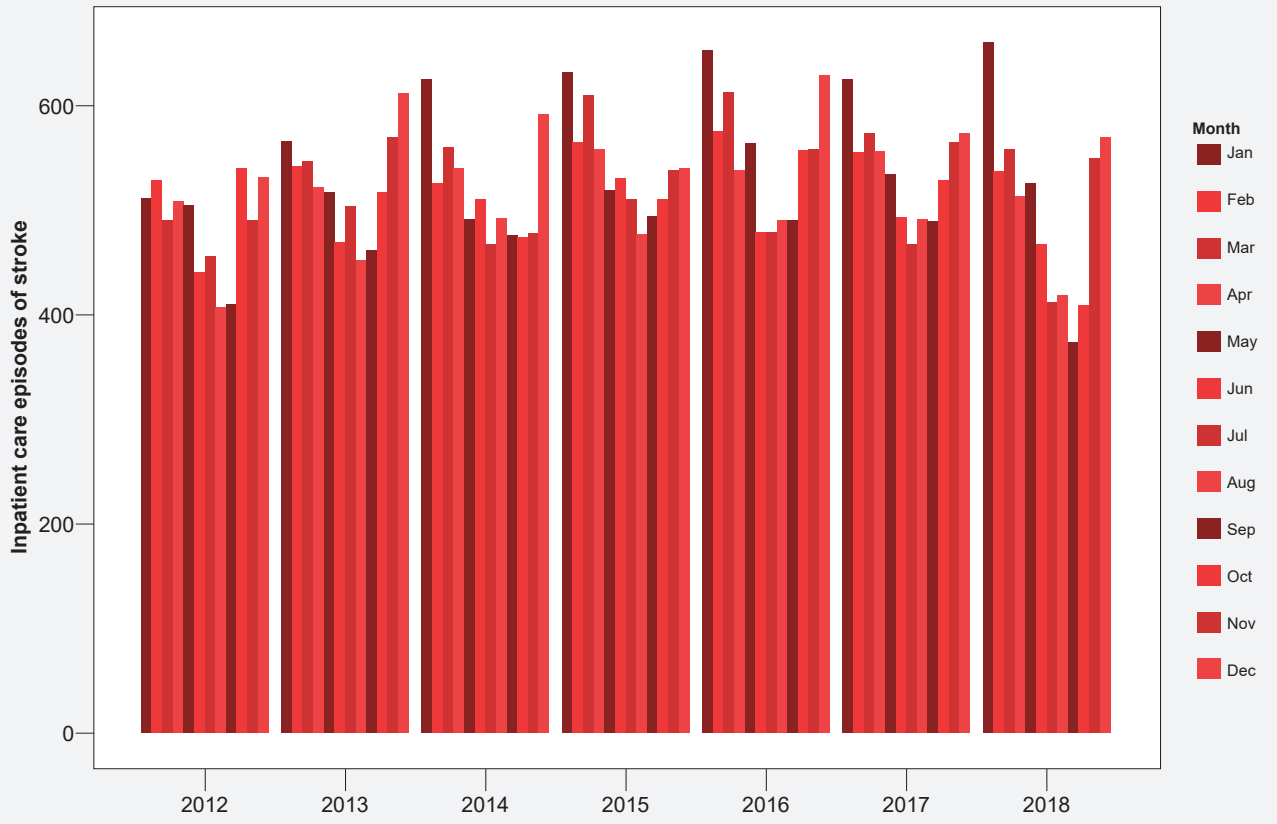

Figure 3 – Grouped bar chart, per month, of the number of inpatient care episodes of stroke involving patients with AF, in mainland Portugal, from Jan 2012 to Dec 2018
Source: figure obtained by the authors based on the BMDH 2012-2018 data

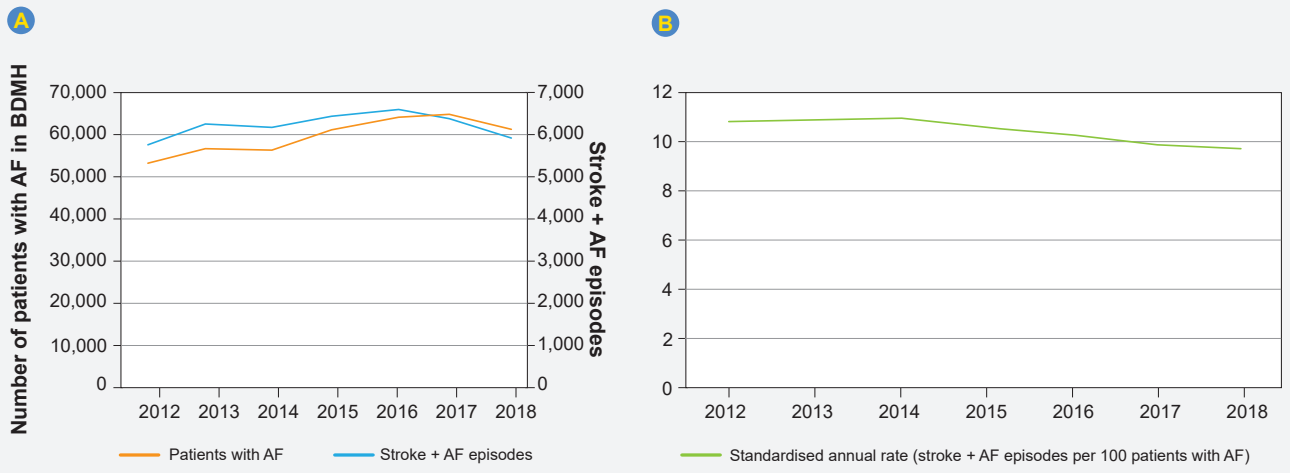

Figure 4 – Standardised annual rate of inpatient care episodes of stroke involving patients with AF in Mainland Portugal, from Jan 2012 to Dec 2018. Time series of the number of patients with AF and the number of inpatient care episodes of stroke + AF in the BDMH, per year (A); standardised annual rate of episodes of stroke + AF (episodes per 100 patients with AF) (B).
Source: figure obtained by the authors based on the BMDH 2012-2018 data

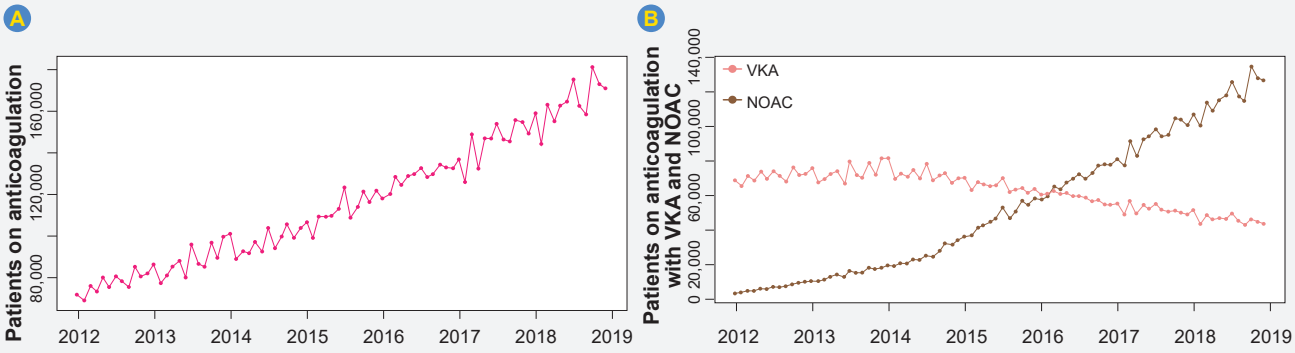

Figure 5 – Chronogram of the series of patients on anticoagulation, in Mainland Portugal, from Jan 2012 to Dec 2018. Oral anticoagulant drugs (total) (A); decomposition into vitamin-K antagonists - VKA (orange) and non-vitamin-K antagonists (brown) (B).
Source: estimate obtained by the authors from statistical data of the national sales of anticoagulant drugs

this case, the categorical variable would assume the value of 0 and the model equation for the counterfactual scenario would become $E_{stroke,t}$ = -0.1376 $X_{1,t}$ + 1.2137 $X_{3,t}$ + N_{t-12} + e_t - 0.5169 $_{et-12}$.

In this counterfactual scenario, an estimated number of 19,908 stroke episodes in AF patients between 2016 and 2018 would be expected (compared to 19,075 episodes estimated by the initial model). Therefore, the effect of the OAC shift between 2016 and 2018 can be quantified in absolute terms as a reduction of 833 stroke episodes in AF patients (4.2%).

DISCUSSION

This study was aimed at assessing the impact of the use of oral anticoagulants on the incidence of AF-related strokes in mainland Portugal.

Considering that a single source for collecting information at an individual level was not available, a multidimensional strategy has been adopted, using aggregate data obtained from two real databases (BDMH and OAC drugs sales statistics).

The descriptive analysis has shown a mostly upward trend in the number of inpatient care episodes of stroke involving AF patients up to 2016, followed by a decrease until the end of the study timeframe. The analysis of the standardised annual rate of inpatient care episodes of stroke involving AF patients per 100 AF patients recorded in the BDMH, on the other hand, showed a downward trend throughout the whole study time frame. In other words, when the effect of the increase in AF prevalence is

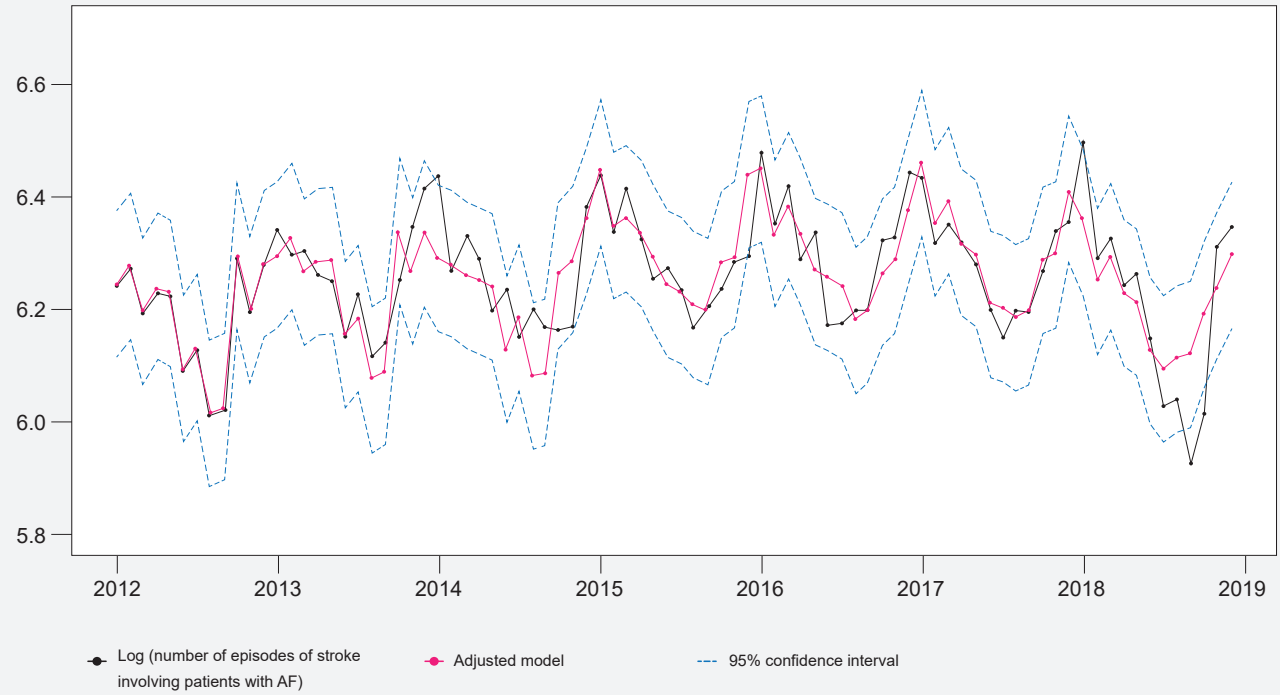

Figure 6 – Timeline of the series of the logarithm of the number of stroke episodes occurring in patients with AF and respective adjusted model. The adjusted model considers three explanatory series: the logarithm of the number of patients treated with OAC, the interaction term between the categorical variable (which assumed a value equal to 1 for observations in the years 2016, 2017 and 2018) and the logarithm of the number of patients treated with OAC, and the number of patients with AF coding.

cancelled out, there is a downward trend in the number of episodes of stroke associated with this arrhythmia.

The increase in the prevalence of AF and AF-related strokes over the past few decades has been described by different authors, using different methodologies to collect epidemiological data.[16-19] Among these, the analysis by Santos *et al*. is worth mentioning, as it reflects the national reality, using the BDMH as a data source. A 32% increase in the number of inpatient care episodes of stroke between 2000 and 2014, with a 138% increase in patients with a secondary diagnosis of AF has been found.[17] These results were explained by the authors, on the one hand, by the effect of the ageing population and greater diagnostic capacity (for example, the use of tests with greater diagnostic accuracy, both in secondary and primary healthcare) and, on the other hand, by the improvement in the conditions for reporting and coding secondary diagnoses in the BDMH.[17] These aspects will also be reflected in this analysis. For this reason, using the number of patients with an AF code in the BDMH as a proxy for the known prevalence of AF seems adequate, reflecting not only the ageing population, but also the possible influence of other factors (greater diagnostic and recording capacity).

The analysis of the time series of inpatient care episodes of stroke in AF patients also suggested the presence of seasonality, in line with other authors, both for the presence of AF-related strokes[20] and paroxysmal AF,[21] suggesting the influence of environmental phenomena (temperature, humidity) or comorbidities with a seasonal pattern (lung infections and exacerbation of chronic obstructive pulmonary disease, for example).

A progressive increase in the use of OAC drugs has been found throughout the study time frame. The sharpest increase in NOAC consumption between 2014 and 2015 was due to the reimbursement by the SNS (in 2014) of the first three NOACs for the prevention of thromboembolic events with non-valvular AF (edoxaban was added in 2016). The shift in the relative composition of the OAC market that occurred in 2016 (Fig. 5B) explained the inclusion of an interaction term between the categorical variable (with a value of 1 for the observations between 2016 and 2018) and the number of patients on anticoagulation.

With the modelling of the number of inpatient care episodes of stroke involving AF patients using a linear regression model with seasonal ARIMA errors, an association between the increase in OAC consumption between January 2012 and December 2018 in mainland Portugal and a decrease in the number of episodes of stroke involving AF patients has been found.

The decrease in the incidence of AF-related strokes is in

line with what has been found by other authors using real-life data. In Stockholm (Sweden), in a retrospective observational study including AF patients, there was an increase in the use of OACs (from 51.6% to 73.8%) and a decrease in the incidence of ischaemic stroke (from 2.01 to 1.17 per 100 person-years) between 2012 and 2017.[18] Using a Poisson model, oral anticoagulation drugs were associated with a 10% reduction in the absolute risk of ischaemic stroke [incidence rate ratio (IRR) of 0. 63 (95% CI: 0.58 - 0.69) before and 0.73 (95% CI: 0.66 - 0.80) upon adjustment for the use of OACs].[18] In England, also using a Poisson model (including adjustment for the prevalence of AF), a 1% increase in the use of OACs was associated with a 0.8% reduction in the weekly rate of AF-related strokes [IRR 0.992 (95% CI: 0.989 - 0.994)].[10]

The feasibility of the analysis was achieved through some concessions and assumptions, leading to limitations. Aggregated data were used, in line with other authors.[10] This may have led to biases in the analysis, the impact of which could not be measured. For example, it is not possible to confirm whether the diagnosis of AF or the onset of anticoagulation drugs occurred before the inpatient care episode of stroke. Similarly, it is not possible to ensure that the cause of stroke episodes in patients diagnosed with AF (AF-related strokes) is the AF itself.

This study was not intended to estimate the prevalence of AF in Portugal or the incidence of stroke. In fact, the methodology used (based on the identification of cases and events in the BDMH) does not include all AF patients, namely AF patients who did not attend the hospital, nor all stroke episodes, namely patients who were not admitted to hospital and inpatient care episodes that occurred in the private sector. Even though the values shown do not correspond to robust absolute estimates of AF prevalence and stroke incidence, this is not critical, as variation over time was the aim of the study.

On the other hand, we were unable to integrate other variables, even in aggregate form, such as baseline thromboembolic or haemorrhagic risk. Another limitation was the assumption that the evolution of the total number of patients on anticoagulation between 2012 and 2018 reflects what happened specifically with AF patients. Although relevant, this assumption seems acceptable, insofar as the other indications for OAC generally refer to restricted use over time (unlike AF). Finally, it was not possible to extend the analysis to 2019 and beyond, given the unavailability of BDMH data for this period.

CONCLUSION

The use of oral anticoagulants was associated with a reduction in the incidence of stroke involving patients with AF in mainland Portugal. This reduction was more relevant between 2016 and 2018, probably due to the increase in OAC consumption following the introduction of NOACs.

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AUTHOR CONTRIBUTION

RA: Writing of the initial draft of the manuscript.

MG, FL: Data analysis.

All the authors have contributed to the conception and design of the study, interpretation of results and critical revision, and all have read and approved the submitted version.

HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical Research Committee, according to the 2013 update of the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

At the time, RA, FL, MB, LSM and JC were members of the Centre for Evidence-Based Medicine Studies (*Centro de Estudos de Medicina Baseada na Evidência* - CEMBE) at the Faculty of Medicine of the University of Lisbon. This research centre is aimed at pre- and post-graduate education and, since 2002, has carried out several clinical, epidemiological and pharmacoeconomic research projects, which have received unrestricted grants from more than 20 pharmaceutical companies, including AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo and Sanofi.

MG and RO had access to the data required to carry out the study through the CEMBE.

DC has received payments or fees for lectures, presentations, speakers' bureaus, manuscript writing or educational events, support for educational activities from Daichi Sankyo, Ferrer, BIAL; DC attended educational meetings and/or participated in conferences or symposia (having received financial support for travel, accommodation and/or hospitality) organised by Bial, Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Merck Serono, Ferrer, Pfizer, Novartis, and Roche.

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