Atrial Fibrillation in Cerebrovascular Disease: National Neurological Perspective

Fibrilhação Auricular na Doença Cerebrovascular: A Perspectiva Neurológica Nacional

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ABSTRACT

Background: Cardioembolism due to atrial fibrillation assumes a dominant etiologic role in cerebrovascular diseases due to its growing incidence, high embolic risk and particular aspects of clinical events caused. Our objectives are to analyze the frequency of atrial fibrillation in patients with ischemic stroke, study the vital and functional impact of stroke due to different etiologies and evaluate antithrombotic options before and after stroke.

Methods: We conducted a retrospective study including patients admitted in a central hospital due to ischemic stroke in 2010 (at least one year of follow-up). Etiology of stroke was defined using the Trial of ORG 10172 in Acute Stroke (TOAST) classification, and functional outcome by modified Rankin scale. We performed a descriptive analysis of different stroke etiologies and antithrombotic medication in patients with atrial fibrillation. We then conducted a cohort study to evaluate the clinical impact of antithrombotic options in secondary prevention after cardioembolic stroke.

Results: In our population (*n* = 631) we found superior frequency of cardioembolism (34.5%) to that reported in the literature. Mortality, morbidity and antithrombotic options are similar to other previous series, confirming the severity of cardioembolic strokes and the underuse of vitamin K antagonists. Oral anticoagulation was effective in secondary prevention independently from post-stroke functional condition.

Conclusions: Despite unequivocal recommendations, oral anticoagulation is still underused in stroke prevention. This study confirms the clinical efficacy of vitamin K antagonists in secondary prevention independently from residual functional impairment.

Keywords: Atrial Fibrillation; Stroke; Cerebrovascular Disorders

RESUMO

Introdução: A cardioembolia por fibrilhação auricular assume particular destaque etiológico nas doenças vasculares cerebrais devido à sua crescente incidência, elevado risco embólico e particularidades dos eventos clínicos causados. São objectivos deste trabalho analisar a frequência da fibrilação auricular numa população de doentes com acidente vascular cerebral isquémico observados num hospital nacional, estudar o impacto vital e funcional dos acidentes vasculares cerebrais causados por diferentes etiologias, e avaliar as opções antitrombóticas prévias e posteriores ao acidente vascular cerebral.

Metodologia: Realizámos um estudo observacional retrospectivo incluindo todos os doentes internados num hospital central por acidente vascular cerebral isquémico em 2010 (pelo menos um ano de seguimento). A etiologia do acidente vascular cerebral foi definida pela classificação Trial of ORG 10172 in Acute Stroke (TOAST) modificada e o resultado funcional pela escala Rankin modificada. Realizámos análise descritiva das diferentes etiologias de acidente vascular cerebral e das prescrições antitrombóticas a doentes com fibrilhação auricular. Realizámos ainda um estudo de coorte para estudar o impacto clínico das opções antitrombóticas em prevenção secundária após acidente vascular cerebral cardioembólico.

Resultados: Na nossa população (*n* = 631) encontramos frequência de cardioembolia (34,5%) superior à relatada na literatura. Os valores de mortalidade e morbilidade além das opções terapêuticas antitrombóticas em pré e pós-Doença Vascular Cerebral são semelhantes aos de outras séries, confirmando a gravidade dos acidentes vasculares cerebrais cardioembólicos e a subutilização dos antagonistas da vitamina K. A anticoagulação oral foi eficaz em prevenção secundária independentemente do estado funcional sequelar após acidente vascular cerebral.

Conclusões: Apesar das recomendações terapêuticas inequívocas a anticoagulação oral continua a ser subutilizada em prevenção de Doença Vascular Cerebral. Confirmamos a eficácia clínica dos antagonistas da vitamina K em prevenção secundária, independentemente das limitações funcionais sequelares.

Palavras-chave: Fibrilhação Auricular; Doença Vascular Cerebral.

INTRODUCTION

Ischaemic cerebrovascular diseases are one of major global mortality and morbidity sources. However, the precise definition of the mechanisms involved in the pathogenesis of the vascular event is crucial, in order to define acute medical care and most importantly the secondary prevention strategy.[1-4] Cardiac embolism is responsible for 15-30% of ischaemic strokes[1-3,5,6] and atrial fibrillation (AF) plays a major role, despite the variety and heterogeneity of cardiac pathologies with an embolic potential. Epidemiological concerns regarding this arrythmia intensify with the exponential increase of its age-related prevalence, with frequencies ranging from 0.1% in <55 year-old adults to 13.7% in octogenarians.[2,7-10] Previous data in the Portuguese population indicate a similar prevalence to international series, affect-

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ing 10.4% of individuals over 80 years old.[11]

This prominent position of AF in current stroke units is explained by its high prevalence, as well as its clinical features related to the associated vascular events. In fact, apart from a capacity for assuming any dimension, cardiac emboli generally manifest as larger strokes than from other cerebrovascular sources[1] giving rise to more severe strokes, low frequency of hospital discharges of asymptomatic patients, high mortality rates and short, medium and long-term recurrences.[5,12-14]

Oral anticoagulants are efficient and usually recommended for cerebrovascular secondary prevention in AF,[15-17] preventing intra-atrial thrombus formation regardless of the rhythm control and obtaining unmatched relative risk reductions as compared to other vascular pathologies.[18] Moreover, in strokes occurring in patients under treatment with vitamin K antagonists (VKA) there is a significant reduction of severity and mortality.[19] However, its clinical use may be restricted by several conditions.

Despite the large demonstration of efficacy of oral anticoagulation in stroke prevention observed in randomized, controlled and double blind trials, the physician who attends patients with AF faces non-selected cases which often represent the same 10-62% of excluded patients in major clinical trials.[18,20-25] Therefore, it seems mandatory to understand our national reality, which the authors chose to study through a Portuguese Central Hospital and its own level A Stroke Unit.

Our objective is to put AF in the national cerebrovascular context, evaluating the cardioembolic stroke frequency and severity in non-selected patients and its implications in the antithrombotic therapy options, trying to provide the vascular physician within the newly available and shortly coming therapeutic options.

MATERIAL AND METHODS

A. Cardioembolic frequency and functional outcome

In order to evaluate cardioembolic frequency and functional outcome upon stroke recovery, we carried out a retrospective study of consecutive patients with a diagnosis of ischaemic stroke admitted in 2010 to a Portuguese Central Hospital. The AF diagnosis had been established after direct visualisation of confirming exams, including previously diagnosed paroxysmal, persistent or permanent forms or during a hospitalisation caused by a stroke. In patients with an AF diagnosis before the stroke, antithrombotic therapy options were confirmed upon clinical file analysis. At three months after the stroke the aetiology of the event was defined according to the Trial of ORG 10172 in Acute Stroke (TOAST) modified classification[26] and functional disability outcome assessed by the modified Rankin Scale (mRS; 0 - 6, with the residual sign or symptom absence being represented by 0 and patient's death by 6).[27] In order to obtain the population frequency we also accounted for the number of recorded AF among the undetermined aetiology strokes, with multiple causes including AF. Whenever functional disability information at 3 months was not available in the follow-up record, data were obtained by telephonic interview.[28] In order to unify the aetiological classification and functional disability results, every case was reviewed by neurovascular clinical research experienced neurologists. In order to compare post-stroke functional disability, we sorted the mRS results at 3 months into independent (mRS: 0 - 2) *vs*. dependent (mRS: 3 - 5), in addition to evaluating mortality in both groups (mRS: 0 - 5 *vs*. mRS: 6).

It should be noted that in our Hospital all patients presenting with an ischaemic stroke are usually hospitalised. We decided to exclude from the study the hospitalised patients with a transient ischaemic attack (TIA) as admission is not systematic, is decided individually and would therefore create a population bias.

B. Antithrombotic therapy in secondary prevention after cardioembolic stroke

In order to evaluate vascular neurology therapeutic decisions in secondary prevention, we studied the subgroup of cardioembolic stroke patients admitted in 2010 to the Stroke Unit/Vascular Ward from the same Hospital (at least one year of clinical follow-up, two years at the most). This was a target population subjected to a homogeneous therapeutic approach with complete demographic, therapeutic and follow-up information recorded in a prospective database. A cohort study was designed for this population, analysing ischaemic stroke, haemorrhagic stroke, any cerebrovascular lesion, death and re-hospitalisation recurrence rates, comparing patients discharged from Hospital following antiaggregant and VKA therapy. The re-hospitalisation causes were defined through analysis of the medical records. For this group of patients, functional disability was evaluated using the mRS scale at the seventh day or at discharge from hospital[27] and cardioembolic risk using the CHA_2DS_2VASc scale.[3] Both scales were applied by experienced neurologists.

C. Statistical methodology

A descriptive analysis was performed, representing an absolute number (percentage) for categorical variables, average (standard deviation) for continuous variables and median (interquartile range) for ordinal variables. In an univariate analysis of this group of patients, we used the χ^2 test for categorical variables comparison, *Student t*-test for continuous and Mann-Whitney U-test for ordinal variables. We performed a binary logistic regression for the multivariate analysis of oral anticoagulation prescription independent predictive variables.

We used the Cox regression analysis in order to evaluate the possible differences between the antithrombotic strategies expressed by the *hazard ratio* (HR) and 95% confidence intervals (95% CI). In accordance with the univariate analysis results comparing antiaggregated and anticoagulated patients, in order to evaluate ischaemic, haemorrhagic or composite ischaemic-haemorrhagic stroke recurrence, we carried out a statistical adjustment for the

CHA_2DS_2VASc score (cardioembolic risk), a scale which includes every recurrence predictive variables discordant for antithrombotic therapy. In order to evaluate the effect on death and re-hospitalisation reduction, we also adjusted for patient functional disability (mRS at the moment of discharge from hospital), a potential bias for the referred analysis.

Re-hospitalisation causes for each antithrombotic strategy were compared using the Chi-square test or Fisher exact test, when appropriate.

Statistical significance was defined for $p < 0.05$.

RESULTS

a) Cardioembolic frequency and functional disability outcome

In our hospital, during 2010, a total of 631 patients were hospitalised for an ischaemic stroke, with a medium age of 73.2 (SD: 12.4), 342 of whom were male (55.2%). Fig. 1 shows the distribution of patients according to the different stroke aetiologies.

Functional disability outcome is presented in Fig. 2. Cardioembolic stroke in 35 patients (16.1%) was responsible for a higher intra-hospital mortality when compared to (i) atherothrombotic stroke: 10 (6.1%), $p = 0.003$ and (ii) with small vessel disease (SVD): one dead patient (0.9%), $p < 0.001$. Cardioembolic lesions in 63 patients (28.9%) were responsible for significantly higher functional disability at three months (mRS ≤ 2) than SVD-related stroke: 84 (73.7%), $p < 0.001$, with no statistical significant differences *vs.* atherothrombotic stroke: 62 patients (38.0%), $p = 0.3$.

b) Pre-morbid antithrombotic therapy

From the 218 patients with cardioembolic stroke, 199 (91.3%) were associated with AF, six (2.8%) with prosthetic heart valves, five (2.3%) with heart failure, four (1.8%) with an emboligenous valvulopathy, two (0.9%) with acute myocardial infarction and two (0.9%) with a patent foramen ovale. We also have to add four patients with AF (0.6% of the total group of patients) classified with an undetermined stroke due to multiple causes including AF, bringing to 203 (32.2%) the total AF number (frequency) in this group of patients. Among the patients with a stroke caused by AF, 130 (65.3%) already had an AF diagnosis before the vascular event occurred. Therapeutic options in the patients with a previous diagnosis of AF at the time of hospital admission were as follows: 95 (73.1%) were not anticoagulated and 35 (26.9%) were treated with VKA; from these 130 patients, only 11 (8.5%) presented a INR value within a therapeutic range on clinical presentation.

c) Antithrombotic therapy decisions and vascular secondary prevention

Considering the 304 patients admitted to our hospital's Stroke Unit/Vascular Ward for an ischaemic stroke, 113 (37.2%) were cardioembolic and 108 (35.5%) were caused by AF. Among the patients with a stroke caused by AF, anticoagulation was prescribed in 76 patients (70.4%).

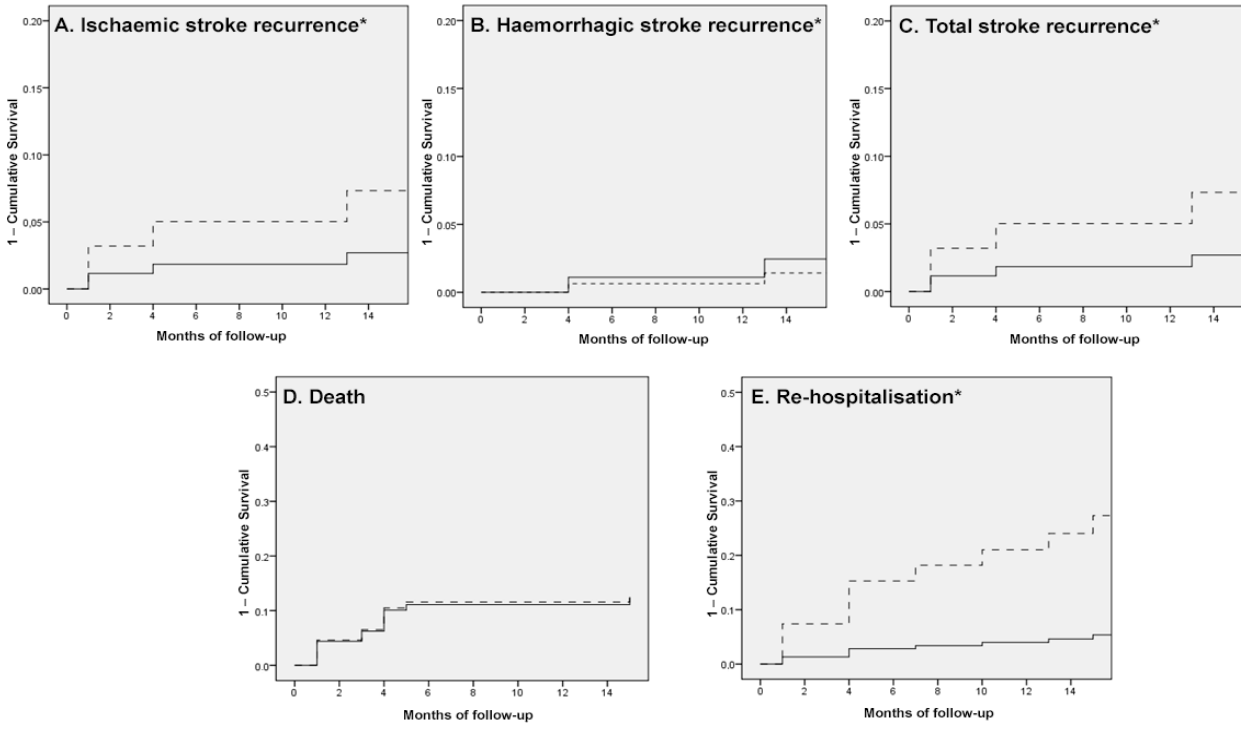

Figure 1 - Histogram representation of the relative prevalence of the different aetiologies of stroke patients hospitalised in 2010, according to the modified TOAST classification. The absolute number and percentage of patients are shown. SVD: small vessel disease; Athero.: atherothrombotic; Card.: cardioembolic; Rare: rare causes; Und.: undetermined causes.

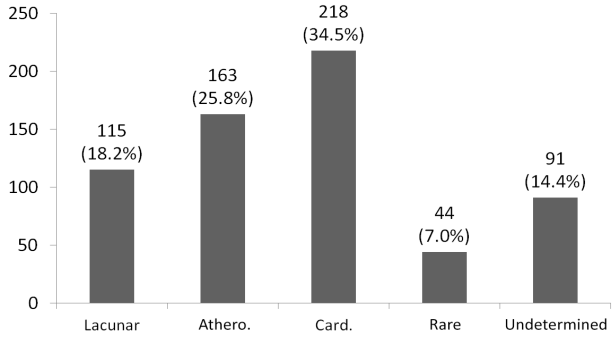

Figure 2 - Percentage histogram of the distribution of functional disability at 3 months, according to the modified Rankin Scale (0 - 6), with reference to the cerebrovascular event aetiology. Dashed line shows dependent vs. independent and dead vs. alive comparisons. *: p < 0.05; **:p < 0.001. Athero.: Atherothrombotic; Card.: cardioembolic; SVD: small vessel disease.

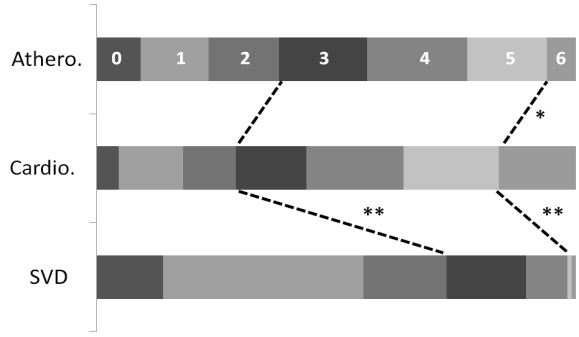

Figure 3 – Cox regression analysis representing oral anticoagulation effect on ischaemic (A.), haemorrhagic (B.) and composite ischaemic + haemorrhagic (C.) stroke recurrence, in addition to the impact on death by any cause (D.) and re-hospitalisation (E.). A, B and C are adjusted for the patient's CHA2DS2VASc score; D and E are adjusted for the patient's CHA2DS2VASc score and modified Rankin Scale score at the moment of discharge from hospital. * : p < 0.05; is: ischaemic stroke; hs: haemorrhagic stroke. Antiaggregated patients are represented by a dotted line and anticoagulated patients by a continuous line.

Table 1 - Clinical and demographic characteristics of hospitalised patients admitted to the Stroke Unit/Vascular Ward in 2010, due to ischaemic stroke secondary to AF. The descriptive analysis of the studied group of patients is presented, as well as the comparison between patients treated with antiaggregation and anticoagulation. The columns on the right represent the multivariate analysis of VKA prescription predictors in secondary prevention.

Variable	Total (*n* = 108)	Univariate analysis			Multivariate analysis	
		Antiaggregation (*n* = 32)	VKA (*n* = 76)	*p*	OR (IC 95%)	*p-adjusted*
Age, average (SD)	**77.1 (10.7)**	82.4 (7.8)	74.7 (10.9)	< 0.001	-	0.299
Female, n (%)	**62 (57.0%)**	25 (78.1%)	37 (48.7%)	0.005	-	0.488
Diabetes Mellitus, n (%)	**22 (20.4%)**	6 (18.8%)	16 (21.1%)	0.786	-	0.058
Hypertension, n (%)	**98 (90.7%)**	31 (96.9%)	67 (88.2%)	0.154	-	0.600
Dyslipidaemia, n (%)	**33 (30.6%)**	10 (31.3%)	23 (30.3%)	0.919	-	0.250
Heart Failure, n (%)	**17 (15.7%)**	6 (18.8%)	11 (14.5%)	0.577	-	0.715
Obesity, n (%)	**5 (4.6%)**	2 (6.3%)	3 (3.9%)	0.603	-	0.986
Smoking, n (%)	**1 (0.9%)**	0 (0%)	1 (1.3%)	0.514	-	1.0
CHA_2DS_2VASc, median (IQR)	**6.0 (2.0)**	6.0 (2.0)	5.0 (2.0)	0.014	-	0.086
High mRS score, median (IQR)	**3.0 (3.0)**	5.0 (1.0)	2.0 (2.0)	< 0.001	0.30 (0.17-0.52)	< 0.001

Legend: SD: standard deviation; IQR: interquartile range; VKA: vitamin K antagonists; OR: odds ratio; CI: confidence interval; age in years.

The reasons for non prescription included severe functional disability in 29 patients (90.6%), the presence of an absolute contraindication, unstable INR or social problems each involving one patient (9.3%). Table 1 presents the clinical and demographic characteristics of the group of patients as well as the comparison between anticoagulated and antiaggregated patients.

Patients with a stroke secondary to AF were followed for an average period of 14.08 months (SD: 7.5) and, during the study period, no losses to follow-up or antithrombotic strategy changes occurred. After an adjustment for cardioembolic risk, anticoagulated patients presented less recurrence of ischaemic stroke (four patients, 11.5% / year *vs*. one patient, 1.3% / year; HR: 7.61; CI 95%: 1.03 – 69.79; *p* = 0.044), with no significant difference regarding the haemorrhagic stroke numbers (one patient, 2.9% / year

Table 2 - Univariate analysis of re-hospitalisation causes in antiaggregated and anticoagulated patients after hospitalisation in the Stroke Unit/Vascular Ward in 2010, caused by AF-related ischaemic stroke.

	Total (*n* = 108)	Antiaggregated (*n* = 32)	Anticoagulated (*n* = 76)	*p*
Total	**25 (23.1%)**	**13 (40.6%)**	**12 (15.8%)**	**< 0.01**
Stroke	**10 (9.3%)**	5 (18.8%)	5 (6.6%)	0.14
Ischaemic	**5 (4.6%)**	4 (12.5%)	1 (1.3%)	0.03
Haemorrhagic	**5 (4.6%)**	1 (3.1%)	4 (5.3%)	1.0
Infection	**10 (9.3%)**	3 (9.4%)	3 (3.9%)	0.36
Respiratory	**6 (5.6%)**	2 (6.3%)	1 (1.3%)	0.21
Urinary	**3 (2.8%)**	1 (3.1%)	2 (2.6%)	1.0
CHF	**7 (6.5%)**	1 (3.1%)	1 (1.3%)	0.51
VT	**3 (2.8%)**	3 (9.4%)	0 (0%)	0.02
DTV	**2 (1.9%)**	2 (6.3%)	0 (0%)	0.09
PE	**1 (0.9%)**	1 (3.1%)	0 (0%)	0.30
Bone fracture	**2 (1.9%)**	0 (0%)	1 (1.3%)	1.0
AMI	**1 (0.9%)**	0 (0%)	1 (1.3%)	1.0
Others	**3 (2.8%)**	1 (3.1%)	1 (1.3%)	0.51

Legend: CHF: congestive heart failure; VT: venous thrombosis; DVT: deep venous thrombosis; PE: pulmonary embolism; AMI: acute myocardial infarction.

vs. four patients, 5.1% / year; HR: 0.57; CI 95%: 0.06 – 5.25; $p = 0.62$), representing a reduction of the total number of cerebrovascular diseases (five patients, 14.4% / year *vs*. five patients, 6.4% / year; HR: 2.78; CI 95%: 1.02 – 8.75; $p = 0.048$) (Fig. 3). We obtained similar mortality numbers (six patients, 15.1% / year *vs*. eight patients, 10.2% / year; HR: 1.05; CI 95%: 0.26 – 4.28; $p = 0.94$) with a significant reduction of re-hospitalisations (13 patients, 45.7% / year *vs*. twelve patients, 16.2% / year; HR: 5.40; CI 95%: 1.87 – 18.0; $p < 0.01$) (Fig. 3). Re-hospitalisation causes are presented in Table 2. Significantly different causes for re-hospitalisation included ischaemic stroke: four patients (12.5%) in the antiaggregation *vs*. one (1.3%) in the anticoagulation therapy group and venous thrombosis (deep venous thrombosis and pulmonary thromboembolism) with an increase in antiaggregated (three patients, 9.4%) *vs*. anticoagulated patients (0, 0%).

DISCUSSION

Even though national cardioembolic stroke related mortality and morbidity data seem to be in agreement with international series,[12-14] a higher cardioembolism frequency than expected was observed in present study.[1,2,5,6] This may be explained by the fact that patients were admitted to a central hospital which consequently biased the sample for higher severity lesions, a fact reinforcing the significant importance of cardioembolism among cerebrovascular lesions causing functional disability. This higher frequency may also be explained by those patients in whom there was co-existence of embolic pathologies, hindering a reliable aetiological definition and the fact that recent studies indicate that at least 25% of cryptogenic strokes might be related to paroxysmal AF non detectable during hospitalisation.[29,30] In addition, the high value of cardioembolic risk in our group of patients is in agreement with the annual recurrence values observed in secondary prevention patients treated with antiaggregation, signalling peculiarities of a hospital population that differ from patients included in major clinical trials.

Not surprisingly, most patients from our study were under antiaggregant therapy before the cerebrovascular event. This constitutes a worrisome reality. In our cohort,

patient therapy, although similar to that described in previous international[31,32] and national series,[33] is not in agreement with the recent guidelines issued by the European Cardiology Society, which does not recommend antiaggregation therapy for AF.[3] We emphasize the significant number of VKA-treated patients with infra-therapeutic INR values at the moment of clinical presentation. These data warn against the risk involved in therapeutic fluctuations associated with VKA, provide compelling evidence for a stricter analytical control and reinforce VKA efficacy when used adequately. In secondary prevention, the number of patients with infra-therapeutic INR was even higher, even though there was some restriction in VKA prescription due to functional disability. Nevertheless, these data are still lower than the US records, although our group of patients represents a population with less functional disability due to its selection bias.[34]

We observed clinical differences in univariate analysis between patients discharged from hospital under anticoagulation *vs.* antiaggregation therapy. Non-anticoagulated patients were elderly, with more severe disability, mainly female and with a higher recurrence risk. The multivariate analysis identified functional disability as a single independent predictor for no oral anticoagulation prescription. Age and functional disability remain as the major constraints for VKA prescription since their introduction. However, even in elderly and disabled patients, the clinical benefit of VKA remains, as supported by our own data and the BAFTA and WASPO studies.[20,22] Another important issue is re-hospitalisation rate reduction in patients treated with VKA, confirming previous findings[35] and to which, beyond cerebrovascular prevention, a reduction in venous thrombosis seems to be a major contributor. These data are not surprising, regarding our group of patients' functional disability as well as the recognized effect of anticoagulation in venous thromboembolism prevention.[36] Patients with mobility problems have difficulty in obtaining an INR and it is hoped that the arrival of the new oral anticoagulants might overcome this constraint.

In our study, female gender is still associated with a lower frequency of anticoagulant prescription, in accordance with previous multicentric studies.[34,37] These differences occur despite a higher recurrence risk in females and in the absence of any differences in oral anticoagulation risk or benefit related to gender. In our group of patients, this association depended on functional disability.

This work has natural limitations due to its objective and design, and it should be interpreted with caution. It is unicentric, observational and non-randomized. Stroke aetiology research has been defined by different physicians and is therefore not homogeneous for every patient, limiting the extrapolation of conclusions to patients with an undetermined aetiology. The non-blinded analysis of clinical results is an inherent constraint to the work; however, the analysed variables (ischaemic/haemorrhagic stroke recurrence, death and re-hospitalisation) are objective and therefore less susceptible to bias. Despite heterogeneity in the univariate analyses between antithrombotic treatments, the subsequent statistical adjustment to clinical results allows a correct interpretation of the obtained data. It is a study involving a relevant series and we believe it does add important information from a national perspective.

CONCLUSIONS

Despite therapeutic recommendations based on evidence arising from several randomised high quality trials since 1984, VKA are still underused. In a group of patients with ischaemic stroke admitted to a Portuguese Central Hospital, we established a high AF frequency, confirming cardioembolism as major cause of cerebrovascular events as well as of mortality and morbidity. Even though from a hospital clinical environment, it was possible to confirm a global efficacy of oral anticoagulation in stroke secondary prevention, regardless of post-morbid functional disability.

CONFLICT OF INTERESTS

The authors declare no conflict of interests regarding this manuscript.

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