Cardioembolic ischemic stroke associated with undertreated atrial fibrillation: an observational study

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SUMMARY

Objectives: To describe the characteristics of patients and to determine the risk factors associated with second Emergency Department visits at 30 and 180 days in sick people admitted to the Emergency Department for cardioembolic stroke with a previous diagnosis of atrial fibrillation.

Methods: Retrospective, observational study of adult patients admitted to the Emergency Department at our institution for cardioembolic stroke from January 1, 2019 to December 31, 2019. All study participants had a previous diagnosis of Atrial Fibrillation, CHADs2-VASc ≥2, and no contraindications for anticoagulants. The patients were retrospectively identified through a database search. A univariate analysis was performed to assess variables potentially associated with readmission (any cause) at 30 and 180 days. All variables with a p<0.2 were included in a multivariate analysis.

Results: During the study period, 547 patients presented to the ED with ischemic stroke and 113 (20.6%) met the study inclusion criteria. Of these, 53 patients (46.9%) did not receive anticoagulant therapy before the stroke and 28 (24.7%) were taking doses lower than recommended in the technical data sheet. The pharmacological stroke prevention strategy was modified in 44 patients (38.9%) at discharge. On the multivariate analysis, diabetes was the only risk factor significantly associated with early readmission to the ED.

Conclusions: Most patients (71.6%) with a previous diagnosis of AF who presented to the emergency department for cardioembolic stroke had not received optimal anticoagulant preventive treatment before the event. Diabetes was the only risk factor associated with early readmission to the Emergency Department.

Key words: **Atrial fibrillation, cerebrovascular stroke, frail elderly, anticoagulant drugs, pharmaceutical services.**

Accidente cerebrovascular isquémico cardioembólico asociado con fibrilación auricular no tratada: estudio observacional

RESUMEN

Objetivos: Describir las características de los pacientes y determinar los factores de riesgo asociados a las segundas visitas al Servicio de Urgencias a los 30 y 180 días en los enfermos ingresados en el Servicio de Urgencias por ictus isquémico cardioembólico con diagnóstico previo de fibrilación auricular.

Métodos: Estudio retrospectivo y observacional de pacientes adultos ingresados en el Servicio de Urgencias del Hospital de la Santa Creu i Sant Pau (HSP) por un ictus cardioembólico desde el 1 de enero de 2019 hasta el 31 de diciembre de 2019. Todos los participantes en el estudio tenían un diagnóstico previo de fibrilación auricular, CHADs2-VASc ≥2, y no tenían contraindicaciones para los anticoagulantes. Los pacientes fueron identificados retrospectivamente mediante una búsqueda en una base de datos del hospital. Se realizó un análisis univariante para evaluar las variables potencialmente asociadas al reingreso (cualquier causa) a los 30 y 180 días. Todas las variables con una p <0,2 se incluyeron en un análisis multivariante.

Resultados: Durante el periodo de estudio, 547 pacientes acudieron a urgencias con ictus isquémico y 113 (20,6%) cumplieron los criterios de inclusión del estudio. De ellos, 53 pacientes (46,9%) no recibían tratamiento anticoagulante antes del ictus y 28 (24,7%) tomaban dosis inferiores a las recomendadas en la ficha técnica. La estrategia de prevención farmacológica del ictus se modificó en 44 pacientes (38,9%) al alta. En el análisis multivariante, la diabetes fue el único factor de riesgo que se asoció significativamente con el reingreso temprano en urgencias.

Conclusiones: La mayoría de los pacientes (71,6%) con diagnóstico previo de FA que acudieron a urgencias por ictus cardioembólico no habían recibido un tratamiento preventivo anticoagulante óptimo antes del evento. La diabetes fue el único factor de riesgo asociado al reingreso temprano en el servicio de urgencias.

Palabras clave: **Fibrilación auricular, ictus isquémico, fragilidad, anticoagulantes, servicios farmacéuticos.**

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INTRODUCTION

Atrial fibrillation (AF) can have many potential consequences, the most disabling of which is stroke. AF is associated with a three-to five-fold increased risk of stroke, and one-quarter of all ischemic strokes[1]. In elderly patients (> age 80), 40% of strokes are associated with AF[2,3]. Stroke prevention strategies in patients with AF include pharmacotherapy (antiplatelet therapy, vitamin k antagonists, and direct oral anticoagulants [DOAC])[1] and left atrial appendage mechanical exclusion. According to clinical guidelines, anticoagulant therapy is the gold standard pharmacological prevention strategy in patients with no contraindications and a CHADs2-Vasc2 score ≥ 2 points[4,5]. Despite the proven value of oral anticoagulants for stroke prevention, studies show that these drugs are frequently underprescribed and/or underdosed, especially in frail patients, mainly due to concerns about drug-drug interactions[6], poor therapeutic adherence, overestimated bleeding risk, older age, and/or risk of falls[7,8].

Drug-related problems (DRP), which have been defined as a "situation that causes the emergence of a negative health effect associated with the drug"[9], are an important and preventable cause of morbidity and mortality in all health care settings and patient populations. Several studies have found that anticoagulants are among the most common medications associated with preventable safety-related DRPs[10,11], and these drugs have also been associated with untreated health-related DRPs, in which health problems occur as a consequence of not receiving the appropriate medical treatment. In one study, nearly one-third of patients with permanent AF who presented to the emergency department (ED) had medication-related negative outcomes, mostly due to undertreatment with antithrombotic therapy (31.1% of cases)[12]. Currently, the proportion of patients admitted to the ED for a stroke-related DRP associated with untreated or undertreated AF is unknown. Similarly, the effect of treatment modification at discharge in this patient population is also unknown.

In this context, the main aim of this study was to describe the characteristics of patients admitted to the ED for cardioembolic ischemic stroke with undertreated nonvalvular AF, a CHADs2-VASc ≥ 2, and no absolute contraindications for anticoagulant therapy. A second aim was to evaluate the effects of treatment modification on readmission rates and the risk factors associated with 30-and 180-day readmission to the ED, with the aim of determining the characteristics of patients who should be targeted for secondary prevention of this DRP.

MATERIAL AND METHODS

Study design

This was a retrospective, cross-sectional, observational study performed in a tertiary care hospital.

Setting and participants

The study was conducted at the ED at an urban teaching, tertiary referral hospital in Catalonia (Spain) that serves a population of approximately 407,000 inhabitants. The approximate annual volume at the ED is 150,000 patients, mainly adults (115,000). Of these, 40% are > age 65 years and more than 30% of them are considered vulnerable (dementia, dependence, active cancer, chronic diseases and comorbidities, and disability).

The study population included patients who presented to the ED for cardioembolic ischemic stroke during the year 2019 (January 1 to December 31). Inclusion criteria were: 1) adult patients (>18 years) with a previous diagnosis of nonvalvular AF or paroxysmal AF; 2) CHADs2-VASc score ≥2, and 3) no absolute contraindications for anticoagulants[1].

Population of the study was identified through a search of the hospital database (Datawarehouse, SAP Business Object).

Variables

From the patients included, the pharmacological stroke prevention strategies used before and after the ischemic stroke were recorded, as well as, age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, ischemic heart disease, chronic kidney disease stage 3 or worse (eGFR <60 mL min 1.73 m^2), active oncological disease, cognitive impairment and the destination at discharge. All the variables were collected by retrospective review of the Clinical Health Shared Record 242 of Catalonia.

Statistical analysis

Chi-squared tests were used to compare categorical data, and t-tests were used to compare mean ages at baseline.

Differences between patients readmitted to the ED 30 and 180 days after discharge versus those not readmitted based on the pharmacological treatment prescribed were evaluated using the chi-square test.

A univariate analysis was performed to identify the variables potentially associated with readmission to the ED at 30 and 180 days. The following variables were assessed: age >80 years; sex; presence of comorbidities, including stage 3 or higher chronic kidney disease (eGFR <60 mL/min 1.73 m^2)[13], heart failure, type II diabetes mellitus, and hypertension; major polypharmacy (≥10 drugs, included medication prescribed as regular and "if needed")[14]; change in anticoagulation therapy; and anticoagulant treatment prescribed at discharge from the ED. In patients who received low-molecular-weight heparin (LMWH) in the ED, this drug was also included in the analysis if the patient continued treatment for > seven days after the first episode or was readmitted to the ED during the course of LMWH treatment.

All variables on the univariate analysis with a p value <0.2 were included in the multivariate analysis to assess the risk factors significantly associated with 30 and 180-day ED readmission for all causes.

All statistical analyses were performed with the Stata 2 Software (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

This study was approved by the Clinical Research Ethics Committee of the Sant Pau Hospital (Hospital Sant Pau; Reference No: IIBSP-COD-2018-25).

RESULTS

During the study period (2019), 547 patients presented at the ED for ischemic stroke. Of these, 113 (20.6%) met the study inclusion criteria and were analysed. The baseline characteristics of these patients are shown in table 1.

Of the 113 patients included in the study, 53 (46.9%) were not receiving anticoagulant drugs prior to the stroke episode. Of these 53 patients, 26 (49%) were receiving antiplatelet therapy (acetylsalicylic acid [n=22] or clopidogrel [n=4]), while the other 27 patients were not receiving any

primary stroke prevention medication, despite the presence of AF.

The other patients (n=60, 53.1%) were taking anticoagulants prior to the ischemic stroke. However, 28 (46.6%) of these patients were taking lower doses than those recommended in the drug's technical data sheet. Thirty-two patients (28.3%) had an ischemic stroke, despite taking the appropriate preventative anticoagulant dose.

These results are summarized in figure 1 and table 2.

The stroke prevention strategy was modified in 44 patients (38.9%) at discharge. A total of 12 patients (10.7%) died during the episode and/or were discharged to an intermediate care centre for palliative or end of life care. In 57 patients, the preventive anticoagulation management strategy was not modified, despite the ischemic event.

The modifications made to the preventative treatment strategy are shown in table 3.

A total of 20 patients (17.7%) returned to the same ED for any cause at 30 days while 36 patients (31.8%) returned between days 31 and 180. Early re-consultation was associated with ischemic and/or haemorrhagic events in one patient (3.3%) (cardioembolic stroke in a patient with secondary prevention with acetylsalicylic acid). Between days 31 and 180, two patients presented at the ED for a second consultation, both for gastrointestinal bleeding (both patients were taking anticoagulants prior to the stroke) and none for ischemic events.

Diabetes is a risk factor associated with early readmission to the ED in the study population. No other risk factors associated with readmission at 30 and 180 days post-discharge were found (table 4).

DISCUSSION

This study was performed to describe the characteristics of patients with a diagnosis of AF admitted to the ED for cardioembolic stroke and to determine the effects of treatment modification on readmission rates and the risk factors associated with readmission. Most of the patients included in this study (71.6%) who presented to the ED for cardioembolic ischemic stroke did not meet the recommendations given in clinical guidelines for preventative anticoagulation therapy[5]. Importantly, undertreatment persisted even after the stroke in a high percentage of patients. On the multivariate analysis, the only risk factor significantly associated with early revisits to the ED was diabetes mellitus. Most of the patients in the study population were old (> age 80), had multiple comorbidities, and were receiving polypharmacy. Cognitive impairment was present in one-third of patients and one in four were institutionalized before the stroke.

According to clinical guidelines, the management of AF, especially in older patients, should prioritise anticoagulant therapy due to the high risk of cardioembolic stroke in these patients. Although age, cognitive impairment, and/or risk of falls do not contraindicate anticoagulation therapy, several studies have shown that these drugs are often underprescribed in these patients, as the findings of our study confirm[7,8].

Table 1. Demographic and baseline clinical characteristics of the patient cohort

Variable	n (%)	Mean (SD)
Age, years		85.52 (7.96)
Sex, female	65 (57.5%)	
Comorbidities		
Hypertension	93 (82.3%)	
Heart failure	18 (15.9%)	
Diabetes mellitus	39 (34.5%)	
Dyslipidemia	60 (53.1%)	
Chronic renal failure	33 (29.2%)	
Active oncological disease	15 (13.3%)	
Cognitive impairment	40 (35.4%)	
Institutionalized patient	29 (25.7%)	
Nº of medications taken regularly at home		8.41 (3.14)
Nº of medications taken regularly at discharge		8.46 (3.09)
Destination at discharge	**n (%)**	
Home	47 (41.6)	
Nursing home	9 (8)	
Long-term health care centre	27 (23.9)	
Hospitalization	23 (20.4)	
Death	7 (6.2)	

SD: standard deviation; n: number.

Table 2. Preventive pharmacological treatment prior to cardioembolic ischemic stroke

Medication prior to ischemic stroke	Number of patients (%)	Underdosing (yes)
None	27 (23.9%)	N/A
AAS	22 (19.5%)	N/A
Clopidogrel	4 (3.5%)	N/A
AVK	29 (25.7%)	13 (44.8%)
DBI	5 (4.4%)	2 (40%)
DXI	18 (15.9%)	6 (33.3%)
LMWH	8 (7%)	7 (87.5%)

AAS: acetylsalicylic acid; DXI: direct Xa inhibitor; AVK: anti-vitamin k anticoagulants; LMWH: low-molecular-weight heparin; DBI: direct thrombin inhibitors; N/A: not applicable.

Figure 1. Preventive pharmacological treatment prior to cardioembolic ischemic stroke

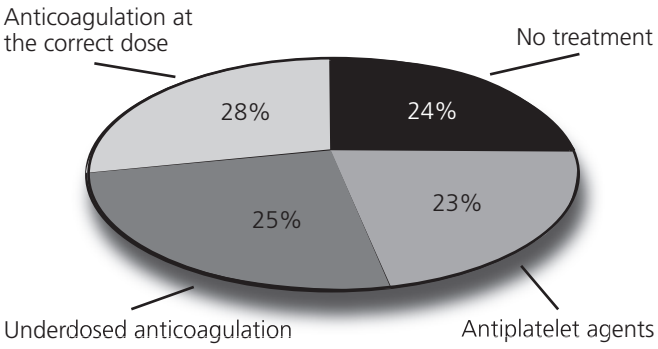

Table 3. Modifications made to the preventative treatment strategy

Medication prior to ischemic stroke	N (%) modification	Medication at discharge (number of patients)
None (n=22)	8 (36.3)	DXI (2), AVK (2), LMWH (4)
AAS (n=22)	6 (27.3)	LMWH (5), DXI (1)
Clopidogrel (n=4)	1 (25)	LMWH (1)
AVK (n =29)	19 (65.5)	LMWH (9), m DXI (6), mDBI (3), AVK(1)
DBI (n=5)	0	
DXI (n=18)	7 (38.9)	LMWH (2), DBI (2), other DXI (3)
LMWH (n=8)	3 (37.5)	DBI (2), DXI (1)

AAS: acetylsalicylic acid; DXI: direct Xa inhibitor; AVK: anti-vitamin k anticoagulants; LMWH: low-molecular-weight heparin; DBI: direct thrombin inhibitors.

Tabla 4. Results of the univariate and multivariate analyses

	30-day post-discharge			180-day post-discharge		
	p-value, univariate analysis	OR (95% CI)	p	p-value, univariate analysis	OR (95% CI)	p
Age > 80 years	0.428			0.603		
Female	0.208			0.481		
Hypertension	0.908			0.985		
Diabetes	0.062	3.92 (1.25-8.22)	0.019	0.388		
Chronic heart failure	0.919			0.197	3.29 (0.55-9.61)	0.191
Dyslipidemia	0.129	0.39 (0.13-1.19)	0.069	0.233		
Chronic renal failure	0.374			0.316		
Cognitive impairment	0.4			0.52		
Institutionalized	0.705			0.384		
Treatment modification at discharge	0.902			0.539		
Anticoagulation at discharge	0.833			0.092	1.17 (0.93-1.49)	0.167

OR: odds ratio; CI: confidence interval.

In our cohort of patients who presented to the ED with cardioembolic ischemic stroke associated with undertreated AF (DRP-related stroke), we found that the risk of early and late ED consultations for any cause did not decrease after switching to another anticoagulant treatment. Nearly 18% of the sample returned to the ED within 30 days for any cause, a slightly lower percentage than observed in other DRP-related visits to the ED among frail patients in our setting. Other studies have found slightly higher rates of second ED consultations at day 30 in patients with different conditions. For example, one study found that 27.5% patients with gastrointestinal bleeding revisited the ED within 30 days of discharge[15], while another study found that 27.9% of those with constipation associated with high anticholinergic burden did so[16]. In a study involving patients with high therapeutic complexity at discharge, 34.8% presented within 30 days of discharge[17].

Our findings suggest that pharmacists could play an essential role within a multidisciplinary team in primary and secondary prevention of DRPs associated with ED visits in frail patients. In cardioembolic ischemic stroke, studies have shown that pharmaceutical care programs improve adherence to anticoagulant therapy[18], quality of life after ischemic stroke[19], and resolve DRP in these patients[20]. Our data strongly suggest that patients with diabetes should be prioritised in secondary prevention programs for DRP-related strokes.

This study shows the consequences associated with the non-use or underuse of anticoagulant therapy in frail patients. Traditionally, the focus of multidisciplinary pharma-

ceutical care programs in elderly patients has been to minimise the risks of safety-related DRPs. Our findings highlight the importance of approaching rational drug use in its three dimensions: necessity, effectiveness and safety, regardless of the type of patient population.

Study strengths and limitations

The main limitation of this study is the single-centre study design, as the findings may not be generalizable to centres located in other regions or countries due to differences in healthcare services, the management of chronic patients in primary care, and in access to certain medicines. All of these differences could influence treatment outcomes in other settings. However, our results are consistent with other studies that have reported underuse of anticoagulant drugs in elderly patients in different health care systems[6]. The main strength of this study is that it is, to our knowledge, the first to specifically assess the proportion of patients admitted to the ED for cardioembolic stroke associated with untreated or undertreated AF.

CONCLUSIONS

The findings of this study show that most patients (71.6%) with a previous diagnosis of AF who presented at the emergency department for cardioembolic ischemic stroke had not received the optimal anticoagulant preventive treatment. Diabetes was the only risk factor significantly associated with early revisits to the ED in this study population. No other risk factors associated with ED readmission at 30 or 180 days were observed.

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Conflicts of interest: The authors declare no conflicts of interest.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item Nº	Recommendation	Page Nº
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4,5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7,8
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	NA
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	MA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	*
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	NA

STROBE Statement—checklist of items that should be included in reports of observational studies (cont.)

	Item Nº	Recommendation	Page Nº
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	10-
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.