Revista Colombiana de Cardiología
Órgano oficial de la Asociación Sociedad Colombiana de Cardiología & Cirugía Cardiovascular
Permanyer

Check for updates

ORIGINAL ARTICLE

# Recurrent stroke due to atrial fibrillation: perspectives on an unsolved problem

## *Ataque cerebrovascular recurrente por fibrilación auricular: perspectivas sobre un problema no resuelto*

*Karen Sánchez-Acosta[1]*, Lizbeth Galeano[1,2], Daniel Villarreal[1,2], Angie Montoya[1], and Hernán Bayona[1,2,3]*

*[1]Medical School, Universidad de los Andes; [2]Department of Neurology, Fundación Santa Fe de Bogotá; [3]Stroke Center, Fundación Santa Fe de Bogotá. Bogotá, Colombia*

## Abstract

**Introduction:** *The cardioembolic stroke recurrence rate could be up to 10% in the first year and increase over time. Evidence is lacking concerning the best therapeutic approach in patients with recurrent stroke while on anticoagulation.* **Objective:** *To explore the relationship between the type of anticoagulant and the composite outcome of ischemic stroke, transient ischemic attack (TIA) or systemic embolism in anticoagulated patients with a recurrent atrial fibrillation-related stroke.* **Materials and method:** *A cross-sectional study involving patients who were treated in the stroke unit from 2014-2019 for atrial fibrillation-related stroke. Patients with clinical records after the index stroke were considered. They were classified as recurrent/non-recurrent and were compared in terms of sociodemographic factors, comorbidities and the oral anticoagulant used. The recurrent group was characterized according to severity, dosing and plasma anticoagulation levels.* **Results:** *60 patients were included (17 with recurrence and 43 without recurrence); in the patients with recurrence, 82.3% of the events were strokes, 17.6% were TIAs, and there were no systemic emboli, with a median recurrence time of 398 days. No relationship was found between the type of anticoagulation and the pre-specified outcomes, although a considerable prevalence of under-dosing and subtherapeutic blood anticoagulant levels was found.* **Conclusion:** *No relationship can be established between the type of anticoagulant and recurrence. Possible explanatory factors were identified; however, the study of these factors and their role in the occurrence of the event is beyond the aim and scope of the present study and should be elucidated in future studies.*

***Keywords:*** *Atrial Fibrillation. Stroke. Anticoagulants. Recurrence.*

## Resumen

**Antecedentes:** *La tasa de recurrencia en ataque cerebrovascular (ACV) cardioembólico podría ser del 10% en el primer año e incrementar con el tiempo. Existe escasa evidencia del mejor enfoque terapéutico en pacientes anticoagulados que presentan un ACV.* **Objetivos:** *Explorar la relación entre el tipo de anticoagulante y el desenlace de ACV isquémico, ataque isquémico transitorio (AIT) o embolia no sistémica en pacientes anticoagulados que presentan ACV recurrente relacionado con fibrilación auricular.* **Materiales y método:** *Estudio de corte transversal en el que se incluyeron pacientes atendidos en la unidad ACV entre el 2014 al 2019 por ACV relacionado con fibrilación auricular. Se consideraron solamente pacientes con*

***Correspondence:**
Karen Sánchez-Acosta
E-mail: kj.sanchez74@uniandes.edu.co

Date of reception: 30-06-2022
Date of acceptance: 18-08-2022
DOI: 10.24875/RCCARE.M22000023

Available online: 20-07-2023
Rev Colomb Cardiol. 2023;30(3):170-177
www.rccardiologia.com

*historia clínica posterior al ACV índice, se categorizaron en recurrentes/no recurrentes y fueron comparados según factores sociodemográficos, comorbilidades y anticoagulante oral usado; el grupo recurrente fue caracterizado en gravedad, dosis y niveles de anticoagulación plasmática.* **Resultados:** *Se incluyeron 60 pacientes, 17 de los cuales fueron recurrentes y 43 no recurrentes. De los pacientes recurrentes, 82.2% fueron ACV, 17.6% fueron AIT y embolia no sistémica con una mediana de tiempo en recurrencia de 398 días. No se encontró relación entre el tipo de anticoagulación y los desenlaces de interés, aunque se halló una prevalencia considerable de subdosificación y niveles de anticoagulante subterapéuticos.* **Conclusión:** *No es posible determinar una relación entre el tipo de anticoagulante y la recurrencia. Se identificó la presencia de posibles factores explicativos; sin embargo, el estudio y rol de estos factores en la aparición del evento van más allá del objetivo y alcance de esta investigación, por lo que debe dilucidarse en futuros estudios.*

***Palabras clave:*** *Fibrilación auricular. Accidente cerebrovascular. Anticoagulantes. Recurrencia.*

## Introduction

Atrial fibrillation (AF), a heart rhythm disorder affecting more than 33 million people worldwide, is considered to be the second cause of ischemic stroke[1]. Anticoagulation is the most effective intervention in patients with AF, as it reduces the risk of stroke by 60%[2], along with all-cause mortality[1,3]. Although anticoagulation is set up as an effective treatment, the risk of stroke from a cardiac embolism to the cerebral circulation is three to five times greater in patients with AF than in patients without this disorder[4]. The risk increases when the patient has had a prior stroke, as a 10-20% risk of recurrence has been calculated in the first year[5] and this risk increases by 2 to 3% per year in patients with a prior stroke, despite anticoagulation[6].

There is little evidence about recurrent stroke due to AF; most is concentrated in observational studies evaluating the risk factors associated with recurrence[7-9] and the optimal time for restarting anticoagulation[8,10,11]. However, the evidence regarding the ideal pharmacological treatment after recurrence in patients on anticoagulation is scant. Within what has been studied from a pharmacological perspective, treatment with oral anticoagulants is recognized as superior to low molecular weight heparin or bridge therapy for preventing recurrent events,[12] and adding antiplatelets may be counterproductive[13]. Another prospective, multicenter cohort study found no differences in terms of recurrence between those who continued with the same anticoagulant and those who changed medication after the recurrence[14]. Furthermore, there are no clinical trials to date suggesting a preference for a particular direct oral anticoagulant (DOAC) or changing from one DOAC to another in these patients[11].

The conclusion from the foregoing is that, so far, the optimal therapeutic strategy for preventing recurrence in patients with treatment failure is unknown[6,14]. The previously discussed knowledge gap is recognized by the scientific societies themselves when they state in their clinical practice guidelines that there is no evidence that changes in pharmacological treatment, such as increasing the anticoagulant dose or adding antiplatelet medications to the treatment plan, are effective in preventing new ischemic events[13]. The American and European clinical practice guidelines indicate that DOACs are the drugs of choice in patients with AF for whom *de novo* anticoagulation is indicated[15,16]. The clinical practice guidelines have no high-quality recommendation for the best treatment approach in patients who have a recurrence while on anticoagulation, but they agree that treatment should be optimized, the dose confirmed, and adherence to medications verified[15,16]. In addition to the existent knowledge gap, only one study was found in the country: a case series on this disease at Fundación Valle del Lili[17].

The objective of this study was to explore the relationship between the type of anticoagulant prescribed and the composite outcome of new ischemic stroke, transient ischemic attack (TIA) or systemic embolism in patients with a prior stroke due to nonvalvular atrial fibrillation (NVAF) on anticoagulant treatment at a tertiary care hospital in Bogotá, Colombia.

## Materials and method

This was a cross-sectional observational study involving patients admitted to the stroke unit at Fundación Santa Fede Bogotá from 2014 to 2019 for an ischemic stroke secondary to NVAF.

Patients with a stroke secondary to NVAF were identified consecutively in the institutional database during the study period. Individuals over the age of 18 who were discharged on anticoagulation after their stroke and who had at least one subsequent readmission were included. Those who had the outcome of interest due to poor adherence to anticoagulation, discontinuing the medication for more than 48 hours or an explicit

statement by family members that it was not taken as prescribed; those with allergies to or intolerance of the anticoagulants, autoimmune diseases, cancer, thrombophilia, other documented stroke mechanisms, another indication for anticoagulation, or in whom no subsequent medical records were available to rule out the occurrence of the outcome of interest were excluded.

After identifying the eligible patients, the institutional hospitalization records were reviewed to rule out a new ischemic stroke, TIA or systemic embolism. Thus, patients were grouped into those who had a recurrence while anticoagulated and those who were anticoagulated with no recurrence.

For all subjects, data was extracted from the medical chart on sociodemographic variables (age and sex), comorbidities, and risk factors (hypertension, diabetes, kidney failure, chronic AF, dyslipidemia, the $CHA_2$ $DS_2$ VASC score and body mass index [BMI]), stroke characteristics and care (NIHSS severity score at admission/discharge, Oxford classification, thrombolysis, hospital stay, modified Rankin at admission/discharge) and anticoagulation prescription at discharge for all patients after the index event. Anticoagulants were classified in two large groups according to their mechanism of action: DOACs (apixaban, rivaroxaban and dabigatran) and vitamin K antagonists (VKAs) (warfarin).

For patients with recurrence, variables were measured on the characteristics of the recurrent event, the type of anticoagulant that was being used during the event and the treatment course after the recurrence. No additional variables were measured for the group without recurrence, apart from the index event variables. The variable of having or not having recurrence was taken as the outcome variable, while the type of anticoagulant was the variable of interest, since we mainly wanted to evaluate the relationship with this exposure. The remaining variables were taken as explanatory.

The Epi Info sample size calculator (version 7.2.4.0) was used to estimate a proportion. A 95% confidence level was used, with 0.05 precision and an estimated proportion of recurrence of 10% according to what is published in the literature, with 350 patients as the estimated sample population, which is the estimated number of cardioembolic strokes treated at the institution during the study period. With all the data, a sample size of 100 patients was estimated and consecutive convenience sampling was agreed on.

To avoid selection bias from differential participation, the patients were included according to the etiology and availability of hospital records, and therefore the investigators were unaware of the outcome. On the other hand, individuals with risk factors for thrombotic events, like thrombophilia and cancer, were not admitted, to avoid confounding bias. All of the extracted clinical variables were operationalized and standardized *a priori* in a dictionary of variables, according to the accepted definitions of the variables of interest (stroke, TIA, systemic embolus, underdosing, and definitions of comorbidities) to avoid measurement bias.

A descriptive analysis was carried out; continuous variables were presented with measures of central tendency and dispersion, while qualitative variables were presented as absolute and relative frequencies. The normality of the variables was proven using the Shapiro-Wilk test. Bivariate analyses were run using Fisher's, T, or Mann-Whitney tests, as applicable, to compare patients with and without recurrence as to stroke risk factors as well as the type of anticoagulant. Statistical significance was established as a p value less than 0.05. All data analyses were done using the STATA SE version 16.0 statistical package.

## Results

After screening 218 patients for a cardioembolic etiology, a total of 60 patients were taken (Fig. 1). Of the patients included, 17 were stroke recurrences and 43 did not have recurrence. Out of all the patients, 50% were women, with an average age of 79.41 years. The main comorbidity in the whole population was hypertension, with a prevalence of 75%, followed by coronary disease. Altogether, 61.7% of the patients already had an AF diagnosis on admission to the hospital, and in the rest, a *de novo* AF diagnosis was made during hospitalization.

Regarding the stroke characteristics, 3.33% of the cases were in-hospital events, 81.67% were acute events, 20% were wake-up strokes and 41.67% had imaging evidence of a prior infarction. Regarding the location, 57.63% had partial obstruction of the anterior circulation and 18.64% had partial obstruction of the posterior circulation, according to the Oxford classification[18]. The total population had an average admission NIHSS of 8.62 points; 49.12% had a modified Rankin (mRS) of 0 at the time of the event and thrombolysis was only performed on 33.33%. The average total hospital stay for the first event was 10.61 days and 3.4 days in the intensive care unit. The most prescribed anticoagulant at discharge was apixaban (46.67%) followed by warfarin (21.7%), dabigatran (18.3%) and rivaroxaban (13.3%). Anticoagulation therapy was instated within the first three days after the stroke in 46.67% of the

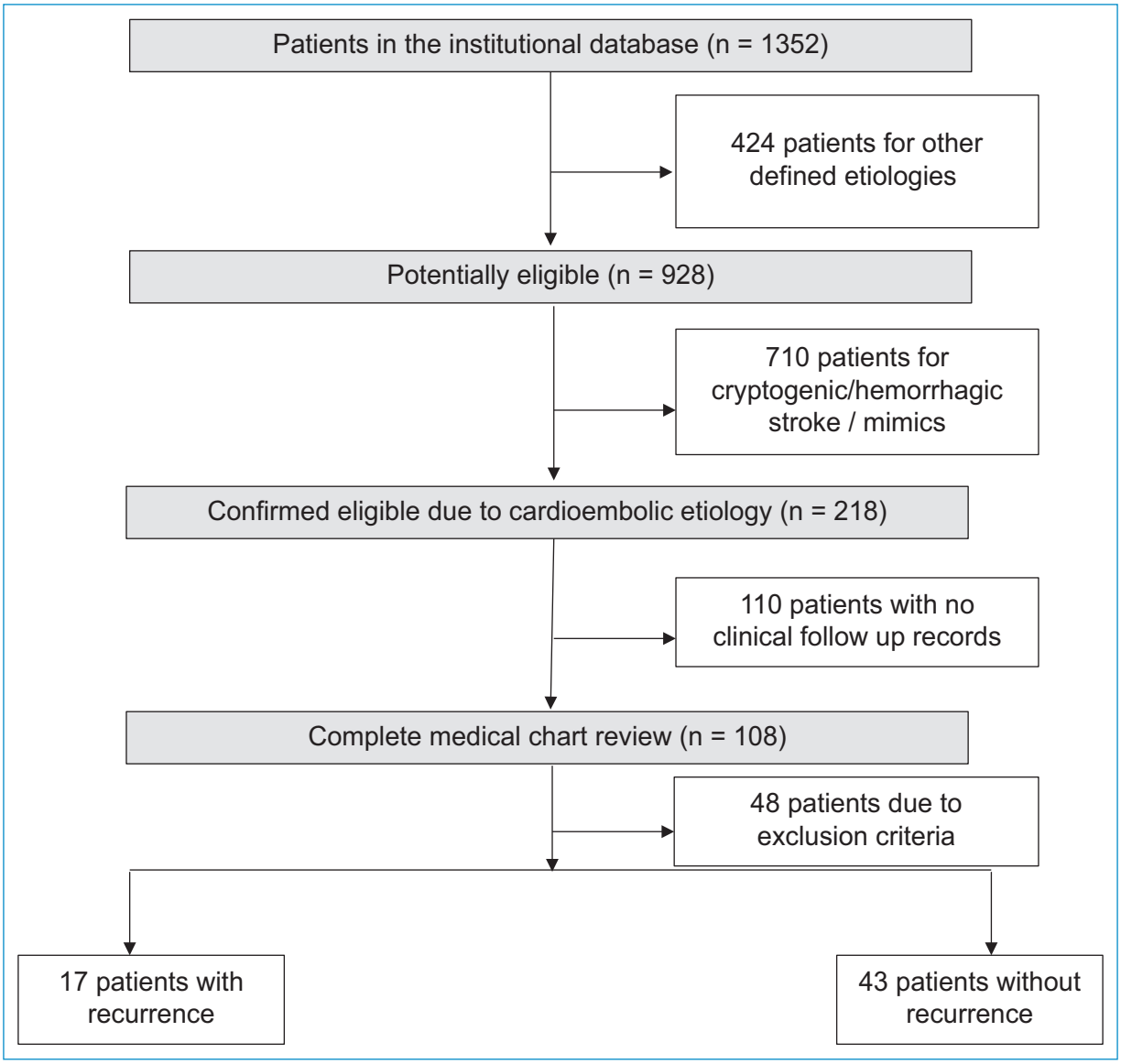


**Figure 1.** Flowchart of the study participants.

patients; 98.33% of the patients received some type of hypolipidemic agent. Ninety percent received education on strokes, the stroke care networks and adherence to anticoagulant medications. Complications, like asymptomatic hemorrhagic transformation (6.67%) and in-hospital urinary tract infections (6.67%) occurred in 20% of the patients.

Altogether, 82.35% of the events were strokes, with an average NIHSS of 6 points; 17.65% were TIAs, and there were no systemic emboli. The median time to recurrence was 398 days; all patients with a recurrence were being anticoagulated with DOACs. Most of the recurrences were on apixaban, with which 64.71% of the patients were anticoagulated. The most remarkable patient characteristics by type of anticoagulant are presented in Table 1. Up to 17.65% were found to be underdosed, taking the glomerular filtration rate, weight or age as the criterion. Levels of anti-Xa were measured in less than half of the patients (41.67%), according to each treating neurologist's decision. In those in whom anti-Xa levels were measured, 57.14% were not anticoagulated. The most common treatment plan after recurrence was to continue with the same management in 56.12% of the patients, although 18.75% were changed to a different DOAC, and another 18.75% had their dose raised. Regarding disability, half of the patients with recurrence

**Table 1.** Patient characteristics by type of anticoagulant

| | Apixaban (n = 11) | Dabigatran (n = 5) | Rivaroxaban (n = 1) |
|---|---|---|---|
| Female sex | 7 (63.64%) | 3 (60%) | 0 (0%) |
| Average age, (SD) | 78.9 (10.36) | 75.8 (7.52) | 89 |
| Average NIHSS of recurrence, (SD) | 6.2 (5.76) | 6.4 (6.54) | 2 |
| GFR<br>> 50<br>30-49<br>< 29 | <br>7 (63.64%)<br>3 (27.27%)<br>1 (9.09%) | <br>3 (60%)<br>2 (40%)<br>0 | <br>0<br>1 (100%)<br>0 |

SD: standard deviation; NIHSS: National Institutes of Health Stroke Scale; GFR: glomerular filtration rate.

had a degree of disability of 4 or more on the Rankin scale, and one person died during the recurrent event.

Comparing patients who had the event of interest with those who did not, the first were more often women, younger, and had a more severe attack index indicated by a higher NIHSS at admission, were more frequently thrombolyzed for the index stroke, had a higher $CHA_2DS_2VASC$ , and a greater prevalence of chronic kidney disease and chronic infarction on imaging, as well as higher BMIs (Table 2), although only chronic infarction on index event imaging and BMI showed significant differences between the groups. No differences were found in the proportion of patients who received a warfarin prescription at discharge after the previous event. However, among those with recurrences, 22.22% were found to have been prescribed warfarin previously, but had been changed to a DOAC when the recurrence occurred.

## Discussion

The proportion of the various types of anticoagulants was found to be similar between both groups. No differences were found in the proportion of patients to whom VKAs or DOACs were prescribed as anticoagulants at discharge after the index event, which would go against a possible relationship between the type of anticoagulant and the outcome of interest. However, as the study was not free of methodological limitations, the presence or absence of a real relationship between the type of anticoagulant used and the outcome of interest cannot be established. Some findings from this analysis could suggest that we are faced with a problem which goes beyond the type of anticoagulant used, like the lack of adherence or underdosing with no underlying reason; however, its real role must be established with further studies.

There was a difference in the therapeutic approach, as none of the individuals with recurrence were being anticoagulated with warfarin. This could reflect medical preferences regarding the use of DOACs, since warfarin is a medication that requires blood monitoring and has major food interactions and precautions[19].

As noted by Seiffge et al.[14], the mechanisms of therapeutic failure may be low adherence to medications, reduced effectiveness of anticoagulants in some individuals, or alternative stroke etiologies. Another explanation for recurrence in anticoagulated patients is the presence of alternative stroke mechanisms. One study found that a greater than 50% stenosis was associated with higher mortality and more recurrences compared with patients without significant stenosis, despite having the same anticoagulation standards and INR levels[20]. Du et al.[21] reported that, in individuals with a prior stroke due to atrial fibrillation, the presence of imaging markers of small vessel disease was related to a high risk of recurrence, and concluded that alternative stroke mechanisms, and not just anticoagulation, could also have an impact on outcomes in this group of patients.

In this study, we tried to control the effect of lack of adherence through the inclusion criteria; however, it is notable that low anti-Xa levels were found in patients with recurrence, although, as a limitation, it should be noted that adherence was self-reported, and therefore not free of information bias. The international guidelines recommend optimizing adherence to anticoagulation when a recurrence occurs while the patient is anticoagulated[3,13]. Low adherence to treatment is considered a public health problem and is the main determining factor in the quality of anticoagulation[22]; the risk of stroke increases 7 to 10% for every reduction in the proportion of days covered by anticoagulation[23]. A study in patients with AF showed that up to 37% of patients were non-adherent to oral anticoagulation[24].

**Table 2.** Baseline characteristics between patients with and without recurrence

| | Patients with recurrence (n = 17) | Patients without recurrence (n = 43) | p |
|---|---|---|---|
| Age* | 77.23 | 80.27 | 0.203 |
| Male sex** | 7 (41.18) | 23 (53.49) | 0.567 |
| Chronic CVA on imaging** | 11 (64.71) | 14 (32.56) | 0.040‡ |
| NIHSS at admission* | 8.85 | 8.54 | 0.832 |
| Hypertension** | 12 (70.59%) | 33 (76.74%) | 0.743 |
| Coronary disease** | 4 (23.52%) | 8 (18.60%) | 0.726 |
| Diabetes** | 3 (17.65%) | 7 (16.28%) | 1.000 |
| Dyslipidemia** | 7 (41.18%) | 19 (44.19%) | 1.000 |
| Kidney disease** | 3 (17.65%) | 3 (6.98%) | 0.338 |
| Average BMI* | 27.87 | 25.14 | 0.025‡ |
| Thrombolysis** | 13 (76.47%) | 27 (62.79%) | 0.375 |
| Use of warfarin** | 4 (23.53%) | 9 (20.93%) | 1.000 |
| Use of DOACs | 13 (76.47%) | 34 (79.07%) | 1.000 |
| Early anticoagulation** | 9 (52.94%) | 23 (53.49%) | 1.000 |
| Hospital stay (days)* | 8.41 | 11.48 | 0.278 |
| CHA2DS2VASC* | 4.47 | 3.97 | 0.438 |
| Discharge teaching | 15 (88.24%) | 39 (90.70%) | 1.000 |

*Wilcoxon rank test.
**Fisher test.
‡$p < 0.05$.
CVA: cerebrovascular accident; NIHSS: National Institutes of Health Stroke Scale; BMI: body mass index; DOACs: direct oral anticoagulants.

Various factors have been related to low adherence to treatment, including age, cognitive level and polypharmacy; furthermore, the rates may be higher in developing countries with few resources and healthcare system access barriers[22]. However, as mentioned previously, the role of adherence to medication or the use of educational interventions to improve it will need to be studied better in future studies.

Another finding was the high prevalence of inappropriate prescription of oral anticoagulants with no indication for an altered dose (based on creatinine clearance, weight or age) among patients with recurrence. According to this study's findings, it reached 17.65%, which was in line with what Stoll et al.[25] reported in a study of patients with stroke due to AF while on anticoagulation. They found that up to one third of these patients were receiving a subtherapeutic DOAC dose, which was directly related to lower serum anticoagulant levels, a greater severity of the recurrent event according to the NIHSS, and less functionality three months after the event.

No differences were found in the proportion of patients with early anticoagulation (1-3 days) among those who had or did not have a recurrence. However, up to 20% of the patients were anticoagulated more than 14 days after the event. To prevent recurrences, the American guidelines recommend beginning anticoagulation between 2 and 14 days after the event[15], while the European guidelines state that it should be done within the first two weeks[16]. The RAF-NOAC study, which evaluated the relationship between the timing of initiation of anticoagulation after the event and the outcome of recurrent stroke or bleeding, showed the harmful effects of delaying anticoagulation, as it reported that the rate of stroke recurrence was 12.4, 2.1 and 9.1% for those who started anticoagulation within the first two days, 3 to 14 days, and more than 14 days after the event, respectively[10].

Overall, patients with recurrence were younger, mostly women, and had a higher prevalence of kidney disease, higher NIHSS and $CHA_2DS_2VASc$ scores, a higher BMI, and evidence of chronic infarction on neuroimaging reports, although only the last two reached statistical significance. These findings are compatible with what was reported in the RAF study, in which a multivariate analysis showed that a high $CHA_2DS_2VASc$ score, a high NIHSS, and the size of the lesion were predictive factors for the composite outcome of ischemia or hemorrhage[12]. Other risk factors for a high rate of recurrence reported in the literature include older age, atrial enlargement, the presence of an intra-atrial thrombus[26], chronic kidney disease[27] and lack of anticoagulation at discharge[28].

One limitation was the small sample size, which affects the power for some variables in the inferential tests, although they were biologically plausible. This small sample size reflects the difficulty in recruiting patients with this condition and with the inclusion criteria. These criteria restricted the number of eligible patients mainly because at least two follow up visits were required, and this was a passive follow up which depended on the demand for healthcare services.

Furthermore, it should be mentioned that, in order to obtain the sample, we included patients who had had

a previous stroke, which is a known risk factor for recurrent events. Another limitation was that the patients' type of AF could not be characterized, as this information was lacking in many of the medical charts. The only classification that could be made was whether the patient already had the diagnosis when the stroke occurred, or if it was identified *de novo* as part of the cardiovascular screening studies, providing an indirect measure of its chronicity. Finally, the selection bias derived from only including patients from a private institution with at least two admissions to the same institution affects the external validity of the study; therefore, caution should be used in extrapolating the results to other populations.

Despite this study's limitations, it must be noted that it contributes to filling the knowledge gap because it provides information on a problem which has been unresolved thus far. Although no conclusions can be drawn regarding the relationship between the type of anticoagulant and recurrence, the descriptive and exploratory focus of this study helps sketch the points which need to be examined further, as well as new research questions to be developed to clarify the role of factors like underdosing, adherence and the timing of delayed anticoagulation. The value of this research also lies in the fact that there are few studies worldwide on the topic; in the Latin American region, some studies have been conducted in Mexico[28,29], and we only have a case series available in Colombia. Furthermore, this condition has been studied in high-income countries with healthcare systems that are very different from the Colombian system. Among other strengths, we present the experience of a high-level center in the approach to this condition, showing the most relevant demographic and clinical characteristics, treatment preferences and difficulty in patient follow up.

## Conclusions

No differences were found in the distribution by type of anticoagulant between those who had a recurrence and those who did not, although a different treatment approach was found in patients with recurrence. The exploratory analysis revealed the existence of factors previously described in the literature, like adherence or underdosing. However, the study of these factors and their role in the occurrence of the event exceeds the objective and scope of this study, and therefore constitutes an opportunity for future study.

## Acknowledgements

The authors would like to thank Dr. Carlos Martínez Rubio and Dr. Eder Moreno Vargas for their help in allowing and facilitating data collection.

## Funding

This study received no financing from any public, commercial or non-profit agency.

## Conflicts of interest

The authors have no conflicts of interest to declare.

## Ethical disclosures

**Human and animal protection**. The authors state that the procedures followed were in line with the ethical norms of the responsible human research committee and according to the World Medical Association and the Declaration of Helsinki.

**Data confidentiality.** The authors declare that they have followed their workplace protocols for patient data publication.

**Right to privacy and informed consent.** The authors obtained approval from the Ethics Committee to analyze and publish routinely obtained clinical data. The patients' informed consent was not required, as this was a retrospective observational study.

## References

1. Piccini JP, Sievert H, Patel MR. Left atrial appendage occlusion: Rationale, evidence, devices, and patient selection. Eur Heart J. 2017;38(12):869-76.
2. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370(26):2467-77.
3. Kirchhof P, Uk C, Uk DK, Uk BC, Germany HD, Heidbuchel H, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the Europ. Eur Heart J. 2016;37(38):2893-962.
4. Kamel H, Healey JS. Cardioembolic stroke. Circ Res. 2017; 120(3):514-26.
5. Saxena R, Lewis S, Berge E, Sandercock PAG, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3.169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. Stroke. 2001;32(10):2333-7.
6. Masjuan J, Salido L, DeFelipe A, Hernández-Antolín R, Fernández-Golfín C, Cruz-Culebras A, et al. Oral anticoagulation and left atrial appendage closure: a new strategy for recurrent cardioembolic stroke. Eur J Neurol. 2019;26(5):816-20.
7. Ogata T, Matsuo R, Kiyuna F, Hata J, Ago T, Tsuboi Y, et al. Left atrial size and long-term risk of recurrent stroke after acute ischemic stroke in patients with nonvalvular atrial fibrillation. J Am Heart Assoc [Internet]. 2017 Aug 15 [cited 2019 Oct 28;6(8). Available from: http://www.ncbi.nlm. nih.gov/pubmed/28862939.
8. Mac Grory B, Flood S, Schrag M, Paciaroni M, Yaghi S. Anticoagulation resumption after stroke from atrial fibrillation. Curr Atheroscler Rep. 2019;21(8):1-11.
9. Arboix A, García-Eroles L, Oliveres M, Massons JB, Targa C. Clinical predictors of early embolic recurrence in presumed cardioembolic stroke. Cerebrovasc Dis. 1998;8(6):345-53.

10. Paciaroni M, Agnelli G, Falocci N, Tsivgoulis G, Vadikolias K, Liantinioti C, et al. Early recurrence and major bleeding in patients with acute ischemic stroke and atrial fibrillation treated with Non-Vitamin-K oral anticoagulants (RAF-NOACs) Study. J Am Heart Assoc [Internet]. 2017 Nov 29 [cited 2019 Oct 30];6(12):1-13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29220330.
11. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. EP Eur. 2021;23(10):1612-76.
12. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, et al. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation: Effect of anticoagulation and its timing: The RAF study. Stroke [Internet]. 2015 Aug [cited 2019 Oct 27;46(8):2175-82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26130094.
13. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare profesionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160-236.
14. Seiffge DJ, De Marchis GM, Koga M, Paciaroni M, Wilson D, Cappellari M, et al. Ischemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. Ann Neurol. 2020;87(5):677-87.
15. Cockroft KM, Gutierrez J, Lombardi-hill D, Kamel H, Meschia JF, Nguyen TN, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack. 2021.
16. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. Guía ESC 2020 sobre el diagnóstico y tratamiento de la fibrilación auricular, desarrollada en colaboración de la European Association for Cardio-Thoracic Surgery (EACTS). Rev Española Cardiol [Internet]. 2021 May 1 [cited 2021 Nov 13;74(5):437.e1-437.e116. Available from: https://www.revespcardiol.org/es-guia-esc-2020-sobre-el-articulo-S0300893220306953.
17. Amaya P. Ataque cerebrovascular isquémico (ACVi) en presencia de anticoagulación: serie de casos. In: XIV Congreso Colombiano de Neurología. 2020.
18. Bamford J, Sandercock P, Dennis M, Warlow C, Burn J. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337(8756):1521-6.
19. Amin A, Keshishian A, Trocio J, Dina O, Le H, Rosenblatt L, et al. Risk of stroke/systemic embolism, major bleeding and associated costs in non-valvular atrial fibrillation patients who initiated apixaban, dabigatran or rivaroxaban compared with warfarin in the United States Medicare population. Curr Med Res Opin. 2017;33(9):1595-604.
20. Nuotio I, Ylitalo A, Lehtola H, Airaksinen KEJ, Hartikainen P, Hartikainen JEK, et al. Stroke recurrence in patients with atrial fibrillation: concomitant carotid artery stenosis doubles the risk. Eur J Neurol. 2017;24(5):719-25.
21. Du H, Wilson D, Ambler G, Banerjee G, Shakeshaft C, Cohen H, et al. Small vessel disease and ischemic stroke risk during anticoagulation for atrial fibrillation after cerebral ischemia. Stroke. 2021;91-9.
22. Yanelli D, Naranjo V, Silvia DO, Bernal P. Adherencia terapéutica a los anticoagulantes orales y su importancia en la enfermedad tromboembólica venosa Adherence to oral anticoagulation drug treatment and its importance in venous thromboembolic disease. Rev Cuba Angiol [Internet]. 2016;17(1):55-70. Available from: http://scielo.sld.cu.
23. Hernandez I, He M, Brooks MM, Saba S, Gellad WF. Adherence to anticoagulation and risk of stroke among medicare beneficiaries newly diagnosed with atrial fibrillation. Am J Cardiovasc Drugs [Internet]. 2020 Apr 1;20(2):199.
24. Salmasi S, Loewen PS, Tandun R, Andrade JG, De Vera MA. Adherence to oral anticoagulants among patients with atrial fibrillation: a systematic review and meta-analysis of observational studies. BMJ Open [Internet]. 2020 Apr 1 [cited 2022 Jun 30];10(4):e034778. Available from: https://bmjopen.bmj.com/content/10/4/e034778.
25. Stoll S, Macha K, Marsch A, Gerner ST, Siedler G, Fröhlich K, et al. Ischemic stroke and dose adjustment of oral Factor Xa inhibitors in patients with atrial fibrillation. J Neurol [Internet]. 2020;(0123456789):1-6. Available from: https://doi.org/10.1007/s00415-020-09795-3.
26. Paciaroni M, Agnelli G, Ageno W, Caso V. Timing of anticoagulation therapy in patients with acute ischaemic stroke and atrial fibrillation. Thromb Haemost [Internet]. 2016 [cited 2019 Oct 27;116(3):410-6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27346426.
27. Sakuta K, Iguchi Y, Sato T, Sakai K, Terasawa Y, Mitsumura H. Chronic kidney disease is independently associated with acute recurrent cerebral infarct in patients with atrial fibrillation. J Clin Neurosci [Internet]. 2017 Jun [cited 2019 Nov 6;40:97-101. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28284577.
28. Arauz A, Ruiz-Navarro F, Barboza MA, Ruiz A, Colin J, Reyes M, et al. Outcome, recurrence and mortality after non-valvular atrial fibrillation stroke: long-term follow-up study. J Vasc Interv Neurol [Internet]. 2017 Dec [cited 2019 Nov 6;9(6):5-11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29445431.
29. Arauz A, Morelos E, Colín J, Roldán J, Barboza MA. Comparison of functional outcome and stroke recurrence in patients with embolic stroke of undetermined source (ESUS) vs. cardioembolic stroke patients. PLoS One. 2016;11(11):e0166091.