ORIGINAL ARTICLE

Discontinuation of Anticoagulation and Associated Factors in Atrial Fibrillation

Discontinuación de la anticoagulación y sus factores asociados en la fibrilación auricular

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ABSTRACT

Background: The aim of the study was to compare if there were any differences between discontinuation of vitamin K antagonists and direct oral anticoagulants and evaluate the factors associated with such discontinuation in newly diagnosed nonvalvular atrial fibrillation.
Methods: We conducted a prospective cohort study. Patients were followed-up for 12 months. Since the assignment of anticoagulation treatment was not randomized, propensity score weighting was used considering the baseline characteristics potentially associated with the exposure and result. Factors associated with the discontinuation of anticoagulant treatment were analyzed with a weighted Cox proportional hazards model.
A total of 379 patients were included; mean age was 78 years (SD ± 9) and 58% were women. Median follow-up was 362 days (interquartile range: 347-370 days) and 1% was lost to follow-up.
Results: The model of time to discontinuation based on inverse probability treatment weighting showed a crude HR of 1.40 (95% CI, 0.79-2.48) and of 1.26 (95% CI, 0.75-2.12) after adjustment for age, type of atrial fibrillation, radiofrequency catheter ablation, bleeding, number of chronic medications and number of medical visits during follow-up for the group treated with direct oral anticoagulants compared with the vitamin K antagonists.
Conclusions: In our setting, anticoagulant discontinuation in nonvalvular atrial fibrillation would not be associated with the type of drug used, age or type of atrial fibrillation. Radiofrequency catheter ablation, bleeding events and the number of medical visits were associated with treatment discontinuation.

Key words: Atrial fibrillation – Anticoagulants - Medication Adherence - Prognosis

RESUMEN

Introducción: El objetivo del estudio fue comparar si existe diferencia en la discontinuación de los antagonistas de la vitamina K y los anticoagulantes directos y evaluar sus factores asociados en la fibrilación auricular de reciente diagnóstico.
Material y métodos: Se realizó un estudio de cohortes prospectivo. El período de seguimiento fue de 12 meses. Debido a que la asignación del tratamiento no fue al azar, se realizó una ponderación por puntaje de propensión considerando las características basales potencialmente asociadas a la exposición y al resultado. Se evaluaron factores asociados a la discontinuación del anticoagulante mediante un modelo de Cox ponderado.
Se incluyeron 379 pacientes con una edad media de 78 años (DE ± 9) y una prevalencia de sexo femenino del 58%. La mediana de seguimiento fue de 362 días (rango intercuartilo: 347-370 días). La pérdida de seguimiento fue del 1%.
Resultados: El modelo de tiempo a la discontinuación del tratamiento anticoagulante ponderado evidenció un HR crudo de 1,40 (IC 95%: 0,79-2,48) y uno ajustado por edad, tipo de fibrilación auricular, ablación por radiofrecuencia, sangrado, cantidad de fármacos crónicos y de consultas médicas durante el seguimiento de 1,26 (IC 95%: 0,75-2,12) para el grupo tratado con anticoagulantes directos en comparación con el tratado con antagonistas de la vitamina K.
Conclusiones: En nuestro medio, la discontinuación de los anticoagulantes en la fibrilación auricular no se asociaría con el tipo de fármaco empleado, la edad o el tipo de arritmia. La ablación por radiofrecuencia, la ocurrencia de sangrado y el número de consultas médicas se asociaron con la discontinuación.

Palabras clave: Fibrilación auricular – Anticoagulantes - Cumplimiento de la medicación - Pronóstico

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INTRODUCTION

Oral anticoagulation has demonstrated to be effective in reducing the incidence of embolic events associated with atrial fibrillation; however, the adherence to treatment is suboptimal. (1-6)

Traditionally, vitamin K antagonists were used for oral anticoagulation. Nowadays, direct inhibitors of thrombin or factor Xa are available as alternative anticoagulants which do not require laboratory monitoring and can be used at fixed doses. Discontinuation of direct oral anticoagulants observed in clinical trials might not represent the real world as they include selected populations within controlled settings. (7-10)

In the health insurance system provided by our hospital, the affiliates requiring cardiology consultations represent an elderly population, with high prevalence of atrial fibrillation with indications for oral anticoagulation. Treatment discontinuation in these cases has not only adverse consequences for the patients but also for the health care system. However, there are no studies available in our setting comparing the discontinuation rate between vitamin K antagonists and direct oral anticoagulants in daily clinical practice.

The aim of the present study was to compare if there were any differences in the incidence of discontinuation between vitamin K antagonists and direct oral anticoagulants during the first year and evaluate the factors associated with such discontinuation in patients with newly diagnosed nonvalvular atrial fibrillation.

METHODS

In this prospective cohort study, the eligible patients were consecutively included between April 2018 and September 2019. The exposed cohort was made up of patients treated with direct oral anticoagulants, while those receiving vitamin K antagonists constituted the unexposed cohort. Each patient was followed-up for 12 months. The research group observed if the anticoagulant prescribed by the treating physicians (external to the study) at the time of diagnosis of atrial fibrillation was discontinued during the follow-up period.

The study was performed in a university-based hospital with 750 inpatient beds and a health care network of 18 outpatient facilities. The electronic medical record is integrated in a patient-centered manner within all areas of care (HIMSS Analytics Stage 6+ certification).

The patients included in the study belonged to the institution health insurance system, and were > 18 years, treated in any hospital setting (coronary care unit, emergency department or outpatient clinics) and had indication for oral anticoagulation due to newly diagnosed nonvalvular atrial fibrillation, with an initial expected use of at least 1 year. Patients who refused to participate, or those treated with oral anticoagulants within the previous 6 months, or with a mechanical valve prosthesis or chronic renal failure with creatinine clearance <30 ml/min (estimated by the MDRD method) were excluded from the study. (11)

An initial telephone interview was made on admission and the electronic medical record was reviewed to collect demographic data, past medical history and chronic medication. During follow-up, telephone interviews were conducted, and medical records were reviewed at 6 and 12 months to detect discontinuation of oral anticoagulation, reasons for discontinuation, and the presence of bleeding or embolic events.

Operative definition of variables

Atrial fibrillation. The following clinical patterns were included: a) paroxysmal, defined as > 1 episodes of AF that terminate spontaneously within 7 days after onset; b) persistent, episodes of AF that lasted ≥ 7 days or required either pharmacologic or electrical intervention to terminate after the initial 48 hours; c) permanent, when cardioversion was not successful or was not attempted; d) undetermined, when none of the above mentioned clinical patterns could not be accurately defined at the time of the initial evaluation because the patients were asymptomatic. Newly diagnosed atrial fibrillation was defined as that diagnosed within the 30 days before starting anticoagulation.

Chronic anticoagulation. Chronic anticoagulation was defined as therapy with vitamin K antagonists (acenocoumarol or warfarin) or direct oral anticoagulants (dabigatran, rivaroxaban or apixaban) initiated during hospitalization or emergency department or outpatient clinic visits, with an initial expected use of at least 1 year.

Discontinuation of anticoagulation. Discontinuation was considered if the patient stopped the medication for at least 30 consecutive days (to exclude temporary interruptions) or in case of switching from one pharmacologic group to the other (vitamin K antagonists and direct oral anticoagulants). The primary outcome was the date of the first discontinuation.

Factors possibly associated with discontinuation. These factors were age, sex, education level, comorbidities (hypertension, diabetes mellitus, dyslipidemia, current smoking, acute myocardial infarction, stroke, congestive heart failure, chronic obstructive pulmonary disease, chronic renal failure), frailty (dependence to perform activities of daily living, number of hospitalizations during the previous year, number of falls during the previous year), thrombocytopenia, concomitant medication predisposing to bleeding (antiplatelet agents), alcohol consumption, history of abnormal liver panel, history of major bleeding, type of atrial fibrillation, health care setting, number of chronic drugs, and ablation procedures, bleeding events and number of medical visits during follow-up. The cost of anticoagulants was considered a constant attribute within each group (high for direct anticoagulants and low for vitamin K antagonists).

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD), or median and interquartile range (IQR), according to their distribution. Categorical variables were expressed as absolute and relative frequencies.

Since the assignment of anticoagulation treatment was not randomized, propensity score weighting approach with inverse probability of treatment weighting (IPTW) was used before analyzing the endpoint. In this procedure, the baseline characteristics potentially associated with the exposure (choice of anticoagulant group) and outcome (discontinuation) were simultaneously considered, as well as those only associated with the outcome. The propensity score is the probability of treatment assignment conditional on observed baseline covariates. The use of IPTW created a synthetic sample in which treatment assignment was independent of measured baseline covariates. (12)

A logistic regression model was performed to estimate the propensity score including the factors possibly associated with discontinuation that were present on admission and those associated with the choice of the anticoagulant. The common area of support or the degree of overlap in the propensity score between both groups of treatment was determined. Covariate balance between the groups was evaluated through the standardized difference in means and proportions and by graphical methods to compare the distribution of continuous variables in the weighted sample.

Weighted Kaplan-Meier curves were constructed to illustrate the discontinuation rate between patients treated with vitamin K antagonists and direct oral anticoagulants and were compared by using the test for weighted data.

A multivariate Cox proportional hazard analysis by IPTW was performed to evaluate those factors associated with the discontinuation of anticoagulant treatment. The covariates included in the model were the baseline characteristics that failed to achieve the balanced distribution after propensity score weighting (double robust approach) and those possibly associated with discontinuation.

The average effect of treatment was used to compare both groups.

A two-tailed p value < 0.05 was considered statistically significant.

All the statistical calculations were performed using STATA 13 (StataCorp LP, College Station, TX) software package.

Ethical considerations

The protocol was approved by the institutional review board and was conducted following the recommendations of the World Medical Association Declaration of Helsinki, the Guidelines for Good Clinical Practice and the current legal regulations on human research in Argentina.

RESULTS

A total of 379 patients were included; mean age was 78 years (SD ± 9) and 58% were women (inclusion flowchart available in Supplementary Material). The baseline characteristics of the population before and after propensity score weighting are compared in Table 1. Figure 1 shows the adequate balance of the baseline covariates, except for age (which required adjustment in the Cox model). The anticoagulants prescribed were acenocoumarol in 192 patients (50.7%), warfarin in 3 (0.8%), dabigatran in 116 (30.6%), rivaroxaban in 14 (3.7%) and apixaban in 54 (14.2%). Only 6 patients had a history of major bleeding that was associated with the indication of a vitamin K antagonist in all the cases (3% vs. 0%, p=0.016). Symptoms were present in 108 patients (55.4%) receiving vitamin K antagonists at the moment of the diagnosis of atrial fibrillation vs. 115 (62.5%) of those receiving direct anticoagulant (p=0.16).

After evaluating the common area of support of IPTW, 343 patients (91% of the total) were incorporated to the model of time to the event. Median follow-up was 362 days (IQR 347-370 days) and 1% was lost to follow-up. Th probability of survival free from discontinuation during follow-up is shown in Figure 2 weighted for the group of anticoagulant. The cumulative incidence of unweighted discontinuation is described in Table 2.

Median time to discontinuation was 154 days (IQR: 81-209 days) in all the patients who stopped or switched the treatment and 158 days (IQR: 107-200 days) in those who stopped treatment after ablation or cardioversion.

For direct oral anticoagulants, time to discontinuation model based on IPTW showed an unadjusted HR of 1.40 (95% CI, 0.79-2.48, p=NS) and of 1.26 (95% CI, 0.75-2,12, p=NS) after adjustment for age, type of atrial fibrillation, radiofrequency catheter ablation, bleeding, number of chronic medications and medical visits during follow-up.

DISCUSSION

Atrial fibrillation is the most common cause of ischemic stroke due to cardiovascular reasons and represents about 20-30% of the cases. (13) Antithrombotic therapy with vitamin K antagonists or direct oral anticoagulants produces a significant reduction in embolic events, morbidity and mortality, constituting a Class IA indication in clinical practice guidelines. (14,15) The last European guideline on the diagnosis and management of AF recommends oral anticoagulation with preference for direct oral anticoagulants over vitamin K antagonists in the absence of moderate to severe mitral stenosis or prosthetic heart valves. This recommendation is based on meta-analyses of the population from randomized controlled clinical trials on anticoagulation (RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF) and is reflected in the global trend towards increased use of direct anticoagulants, (16-21) although the data available in our country show a different reality. (22).

In our study, patients treated with direct oral anticoagulants were relatively younger, were functionally more independent, had lower serum creatinine levels, less use of chronic drugs, less fall events and hospitalizations in the previous year, and lower CHA_2DS_2-VASc score. When the population of the pivotal studies (RE-LY, ARISTOTLE and ROCKET-AF) was compared with our patients, these studies demonstrated male predominance (62% vs. 42%), younger patients (mean age 71 vs. 78 years) and a lower prevalence of comorbidities (median CHA_2DS_2-VASc 2 vs. 3), which is consistent with the differences reported between patients participating in clinical trials and those in real-world registries. (23-25)

Discontinuation of anticoagulation was 24.6% in the direct oral anticoagulant group and 15.6% in the vitamin K antagonist group; these findings are similar to those emerging from pivotal studies, which show that discontinuation of anticoagulation varies between 15 and 25% with direct oral anticoagulants and between 10 and 27% with vitamin K antagonists. (25) Time to discontinuation model based on IPTW, which considered the baseline characteristics of the patients included, did not demonstrate significant differences

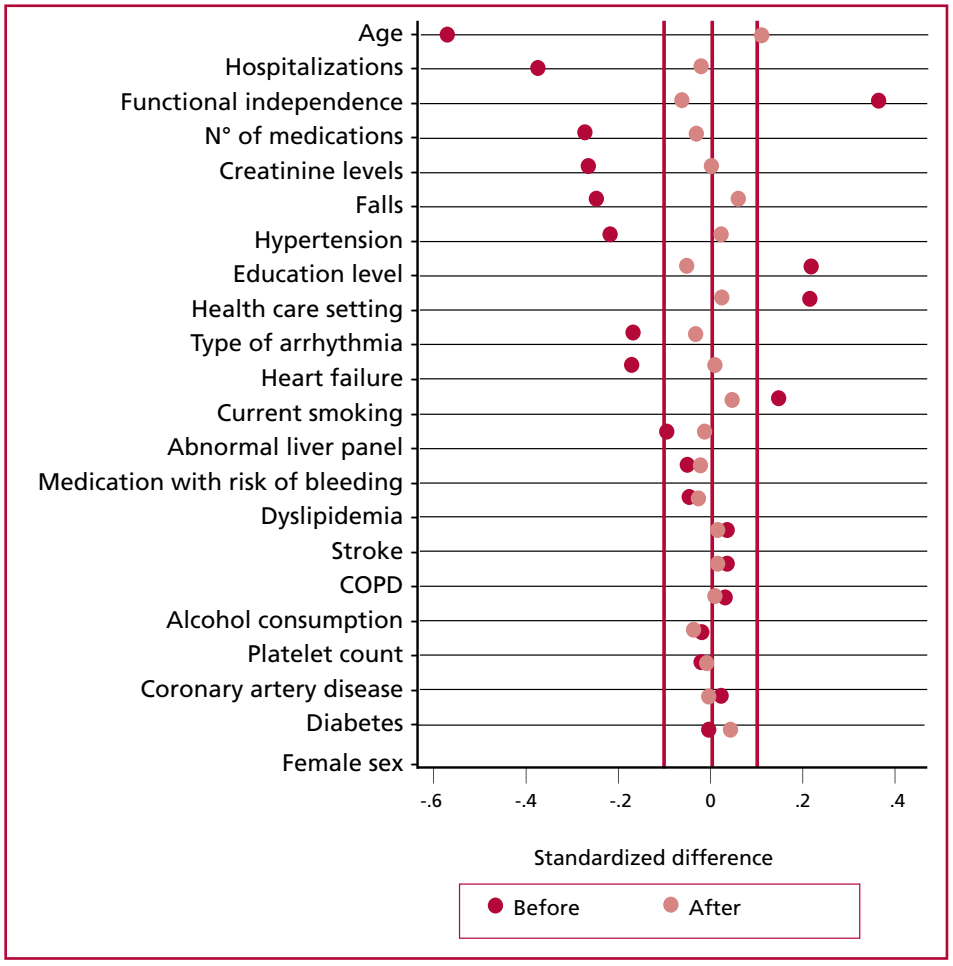
Table 1. Baseline characteristics of the patients before and after IPTW

	Total n=379	Vitamin K antagonists n=195	Direct oral anticoagulants n=184	Unweighted p values	Standardized difference by IPTW
Age, mean (SD), years	78 (9)	81 (8)	75 (8)	<0.001	0.107
Female sex, %	58	59	56	0.56	0.041
Education level; %					
None	6.9	9.2	4.3	0.11	–0.052
Primary	33.8	37.9	29.3		
Secondary	35.6	34.9	36.4		
University	23.7	17.9	29.9		
Medication associated with bleeding. %	18.5	19.5	17.4	0.6	–0.025
N° of chronic medications, median (IQR)	5 (4-6)	5 (4-7)	4 (3-6)	<0.001	–0.035
N° of falls during the last year, median (IQR)	0 (0-0)	0 (0-1)	0 (0-0)	0.002	0.057
N° of hospitalizations during the last year, median (IQR)	0 (0-1)	0 (0-1)	0 (0-0)	<0.001	–0.023
Activities of daily living requiring help ‡, %					
0-1	80.2	69.2	91.8	<0.001	–0.064
2-4	13.7	21.5	5.4		
5-8	6.1	9.2	2.7		
Regular alcohol consumption, %	6.3	5.6	7.1	0.57	0.008
Current smoker, %	5.3	3.6	7.1	0.13	0.044
Dyslipemia, %	47.4	49.2	45.4	0.45	–0.032
Hypertension, %	72.6	79.5	65.2	0.002	0.021
Diabetes, %	10	9.7	10.3	0.85	–0.006
History of heart failure, %	13.5	17.9	8.7	0.008	0.011
History of myocardial infarction, %	6.9	7.7	6	0.51	–0.015
History of stroke, %	5.8	5.1	6.5	0.56	0.010
COPD, %	2.1	2.1	2.7	0.67	0.011
Abnormal liver panel, %	13.7	14.4	13	0.71	–0.012
Platelet count, mean (SD)	224.429 (74.978)	223.270 (75.279)	225.657 (74.843)	0.76	–0.040
Creatinine level mg/dl, mean (SD)	0.93 (0.28)	0.98 (0.31)	0.89 (0.23)	<0.001	0.001
Type of atrial fibrillation, %					
Undetermined					
Paroxysmal	48	44.1	52.2	0.021	–0.032
Persistent/	33	31.8	34.8		
Permanent	19	24.1	13		
Health care setting, %					
Outpatient clinic	29.8	27.7	32.1	0.001	0.023
Emergency department	49.3	44.1	54.9		
Intensive care	20.8	28.2	13		
HAS Bled, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	.31	†
CHA_2DS_2-VASc, median (IQR)	3 (3-4)	4 (3-4)	3 (2-4)	<0.001	†

SD: standard deviation IQR: interquartile range COPD: chronic obstructive pulmonary disease IPTW: inverse probability of treatment weighting
† The individual components were considered for weighting
‡ Activities of daily living: preparing meals, shopping, transportation, making phone calls, cleaning the home, doing laundry, managing finances and managing medication.

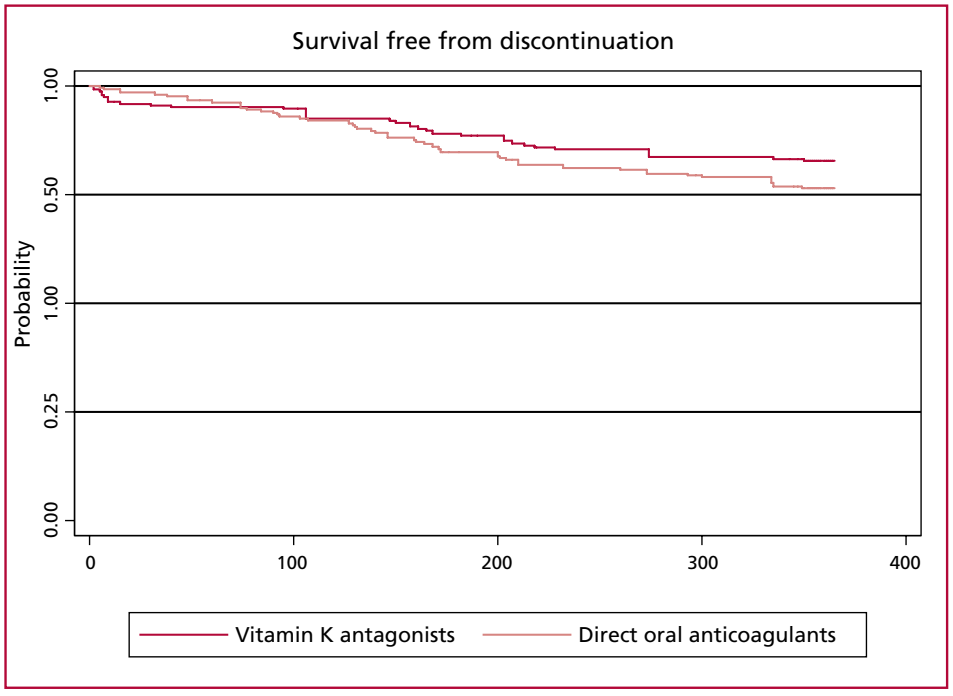
between the groups in crude HR and HR after adjustment for age, type of atrial fibrillation, radiofrequency catheter ablation, bleeding, number of chronic medications and medical visits during follow-up.

The main reason for discontinuation of anticoagulation in the group using vitamin K antagonists was the high risk of bleeding. In the group using direct oral anticoagulants, treatment was stopped due to the radiofrequency catheter ablation of the arrhythmia or cardioversion, although discontinuation was only



COPD: chronic obstructive pulmonary disease

Fig. 1. Standardized difference in means and proportions of the baseline characteristics before and after IPTW.



p value = 0.25 (Wald test)

Fig. 2. Kaplan-Meier curves of discontinuation by group of anticoagulant after IPTW

Table 2. Incidence of unweighted events during follow-up

	Vitamin K antagonists n=166	Direct oral anticoagulants n=177	Unweighted p values
Discontinuation of anticoagulation, n (%)	26 (15.8)	43 (24.6)	0.043*
Type of discontinuation, n (%)			
Cessation	14 (54)	24 (56)	0.87
Switching to another drug	12 (46)	19 (44)	
Reason for cessation, n (%)			
High risk of bleeding	10 (71)	2 (11)	
Bleeding event	1 (7)	5 (26)	
Intolerance	0 (0)	1 (5)	
Postablation/postcardioversion	3 (21)	11 (58)	0.004
Reason for switching, n (%)			
High risk of bleeding	2 (17)	0 (0)	
Intolerance	1 (8)	2 (10.5)	<0.001
Financial	0 (0)	15 (79)	
Other †	9 (75)	2 (10.5)	
Drug switched to, n (%)			na
Acenocoumarol			
Warfarin		18 (95)	
Dabigatran	2 (17)	1 (5)	
Rivaroxaban	3 (25)		
Apixaban	7 (58)		
Ablation, n (%)	3 (1.8)	14 (7.9)	0.009
Embolism, n (%)	5 (3)	1 (0.6)	0.084
Bleeding, n (%)	4 (2.4)	8 (4.5)	0.29
Site of bleeding, n (%)			
Gastrointestinal	1 (25)	5 (62.5)	
Vaginal and urinary tract	1 (25)	0 (0)	
Epistaxis	1 (25)	0 (0)	0.083
Central nervous system	1 (25)	0 (0)	
Undetermined	0 (0)	3 (37.5)	
Bleeding severity, n (%)			
Minimal	2 (50)	2 (25)	
Minor	0 (0)	2 (25)	0.058
Major	0 (0)	4 (50)	
Life-threatening	2 (50)	0 (0)	
Mortality, % (n)	7 (4.2)	3 (1.7)	0.17

* Unweighted Cox model for univariate analysis
† Mechanical valve prosthesis in case of direct oral anticoagulants and suboptimal/labile INR in case of vitamin K antagonists

observed in some patients undergoing catheter ablation (6/17) and was decided by the primary care physician during follow-up. The main reasons for switching oral anticoagulation from one group to the other were suboptimal/labile INR in the group treated with vitamin K antagonists and economic reasons in the group treated with direct oral anticoagulants.

When we compared the reasons for discontinuation observed in our study with those of the pivotal studies with direct oral anticoagulants, we noted that these studies lacked information probably because the main purpose of these trials was to test the hypothesis of noninferiority or superiority for stroke prevention.

In 2016, Yao et al. published the results of a retrospective cohort of patients belonging to a health insurance plan treated with anticoagulants due to atrial fibrillation. (26) In this population, adherence to treatment with vitamin K antagonists was 40.2% at one year and 47.5% with direct oral anticoagulants. According to these authors, the low percentage of ad-

	95% CI	95% CI	*p* values
Direct oral anticoagulants*	1.26	0.75-2.12	0.38
Age	0.97	0.94-1.01	0.11
Type of AF			
Paroxysmal	1.26	0.71-2.27	0.43
Persistent/Permanent	1.11	0.50-2.46	0.80
Catheter ablation	3.15	1.36-7.31	0.008
Bleeding events	3.58	1.97-6.51	<0.001
N° of medications	1.01	0.92-1.13	0.72
N° of medical visits	0.91	0.84-0.99	0.032

Table 3. Model of time to anticoagulant discontinuation by ITPW

* Compared with vitamin K antagonists
AF: Atrial fibrillation

herence to treatment could be explained by the fact that oral anticoagulants are purely preventive and address no symptoms.

In the ORBIT-AF study, the most reported reasons for discontinuation of treatment with vitamin K antagonists were physician preference, patient refusal, and bleeding events. This reason is similar to our findings for the same group of anticoagulants.

Although our study was not designed to evaluate the safety and efficacy of anticoagulation therapy, there were no fatal bleeding events or intracranial bleeding with any of the direct oral anticoagulants.

We found ablation was more common in the group treated with direct oral anticoagulants. Probably these patients were less frail and for this reason an invasive strategy was chosen for rhythm control.

Among the limitations of this study, its single-center design included only patients belonging to a health care insurance program, so the choice of anticoagulant and its discontinuation may reflect a different reality from that of other health care centers and regions of the country. Given the effect size and the number of events observed, the statistical power was <80%. As the study was observational, treatment assignment was not randomized. To overcome these limitations, a propensity score weighting approach was used before analyzing the endpoint.

In our setting, anticoagulant discontinuation in nonvalvular atrial fibrillation would not be associated with the type of drug used (direct oral coagulation or vitamin K antagonist), age or type of atrial fibrillation. Radiofrequency catheter ablation, bleeding events and number of medical visits during follow-up are associated with treatment discontinuation.

Conflicts of interest

Boehringher Ingelheim provided an unrestrictive grant for the administrative costs of the study.

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