ORIGINAL ARTICLE

Predictors for the Use of New Direct Anticoagulants in Atrial Fibrillation and Their One-Year Adherence

Predictores de la elección de nuevos anticoagulantes directos en la fibrilación auricular y su adherencia al año

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ABSTRACT

Background: Men with CHA_2DS_2-Vasc score ≥1 or women with CHA_2DS_2-Vasc score ≥2 and atrial fibrillation/flutter have high indication of antithrombotic treatment.
Objective: The aim of this study was to analyze the prevalence of anticoagulant therapy in this population, to find predictors for the use of new oral anticoagulants and to analyze the one-year adherence to treatment.
Methods: A total of 484 consecutive patients were included in the study. Exclusion criteria were in-hospital mortality (n=12) and CHA_2DS_2-Vasc score of 0 in both genders and 1 in women (n=67). Finally, 405 patients were analyzed with median age of 76 years, 46% women, 76% hypertensive, 25% diabetic, 10% with previous stroke and 30% with history of atrial fibrillation/flutter.
Results: A rhythm control strategy was used in 66% of cases and 293 patients were anticoagulated at discharge (72%). Among anticoagulated patients, 63.5% received new oral anticoagulants, especially those who were younger (74 vs. 79.5 years, p=0.001), with lower history of stroke (5.8% vs.18%, p<0.001), lower median CHA_2DS_2-Vasc (3 vs.4, p<0.01) and HAS-BLED (1 vs. 2, p<0.01) scores and with sinus rhythm at discharge (73.8% vs. 54.7%, p<0.001). Among 165 patients discharged with new oral anticoagulants and followed up for one year, 55.7% adhered to the indicated new oral anticoagulant, 29.69% had discontinued the anticoagulation treatment and 14.5% had switched to acenocoumarol.
Conclusions: The study shows that only 70 of patients are anticoagulated at discharge. New oral anticoagulants were used in more than half of cases, especially in patients at lower clinical risk. At one-year follow-up, 6 out of every 10 patients with indication of new oral anticoagulants at discharge continue this treatment, 1 switches to acenocoumarol and 3 abandon anticoagulant therapy.

Key words: Atrial fibrillation – Atrial flutter – Anticoagulants - Adherence

RESUMEN

Introducción: Los hombres con CHA_2DS_2-Vasc ≥ 1 o las mujeres con CHA_2DS_2-Vasc ≥ 2 y fibrilación/aleteo auricular tienen indicación de tratamiento antitrombótico al alta.
Objetivos: Analizar la prevalencia del uso de anticoagulantes en esta población; hallar predictores del uso de nuevos anticoagulantes orales; y analizar la persistencia al año del tratamiento con nuevos anticoagulantes orales.
Material y métodos: Pacientes consecutivos: 484. Los criterios de exclusión fueron la muerte intrahospitalaria (n: 12) y CHA_2DS_2-Vasc de 0 en ambos géneros y de 1 en mujeres (67 pacientes). Los pacientes analizados fueron 405. Edad mediana: 76 años, género femenino: 46%, HTA: 76%, diabetes: 25%, accidente cerebrovascular previo: 10%, antecedentes de fibrilación/aleteo auricular: 30%.
Resultados: Estrategia de control de ritmo: 66%. Fueron anticoagulados al alta 293 pacientes (72%). Entre los pacientes anticoagulados, los nuevos anticoagulantes orales fueron los más utilizados: 63,5%, especialmente en los menos añosos (74 versus 79,5 años, p: 0,001), con menos antecedentes de accidente cerebrovascular (5,8% versus 18%, p < 0,001), menor CHA_2DS_2-Vasc mediana (3 versus 4, p < 0,01) y HAS-BLED mediana (1 versus 2, p < 0,01) y en más pacientes con ritmo sinusal al momento del alta (73,8% versus 54,7%, p < 0,001). De los 165 pacientes externados con nuevos anticoagulantes orales y seguidos al año, el 55,7% mantuvieron el nuevo anticoagulante oral indicado, un 29,69% habían discontinuado la anticoagulación y el 14,5% rotó a acenocumarol.
Conclusiones: En nuestro trabajo, se anticoagula al alta solo al 70% de los pacientes. Se utilizaron nuevos anticoagulantes orales en más de la mitad de los casos, especialmente en los pacientes de menor riesgo clínico. Al año de seguimiento, cada 10 pacientes medicados al alta con nuevos anticoagulantes orales, 6 persisten con ese tratamiento, 1 rota a acenocumarol y 3 dejan de estar anticoagulados.

Palabras clave: Fibrilación auricular- Aleteo atrial - Anticoagulantes - Adherencia

Abbreviations

AF/AFl	Atrial fibrillation/atrial flutter	NOAC	New oral anticoagulants
IHD	In-hospital mortality		

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INTRODUCTION

In patients admitted to a coronary care unit due to atrial fibrillation or atrial flutter (AF/AFl) and with a CHA_2DS_2-Vasc score ≥1 in men or ≥2 in women, it is usually recommended to start antithrombotic therapy at discharge. (1) New oral anticoagulants (NOAC) are effective and safe, have lower risk of intracranial bleeding, are easy to administer and do not require laboratory controls or periodic visits to the hematologist, thus becoming a good treatment option. Current clinical practice guidelines recommend their use over vitamin K antagonists, provided there are no contraindications for their use. (2) However, their use in clinical practice may be restricted due to their high cost or the fear of lack of antidotes.

OBJECTIVES

The aim of this study was to analyze the use of anticoagulation at discharge after hospitalization for AF/AFI, to analyze the clinical characteristics of patients that determine the use of oral antithrombotic therapy and the choice of NOAC, and to evaluate the 1-year adherence in the use of NOAC in our population.

METHODS

Patients admitted to two coronary care units of private institutions due to AF/AFI were prospectively and consecutively included in the study. After calculation of the CHA_2DS_2-Vasc score, men with CHA_2DS_2-Vasc ≥1 and women with CHA_2DS_2-Vasc ≥2 were selected for the analysis.

The frequency of antithrombotic treatment indication at discharge from the coronary care unit was calculated. Predictors of NOAC indication at discharge were analyzed in anticoagulated patients. Face to face or telephone patient monitoring was performed to obtain information regarding the continuation or not of NOAC use at one year, and in the case of discontinuation or change of anticoagulant treatment, the reasons for this situation. Patients of both genders with CHA_2DS_2-Vasc score = 0, women with CHA_2DS_2-Vasc score = 1 and patients who died in the coronary care unit were excluded from the study. In the analysis of treatment continuation with NOAC at one year, patients who died during that period were also excluded.

Statistical analysis

Discrete variables are presented as percentage and continuous variables as mean ± standard deviation if their distribution was normal or as median and 25%-75% interquartile range if the distribution was non-normal. Variables were compared using Student's t, Wilcoxon, chi-square or Fisher's exact tests, as appropriate. A univariate analysis was performed to determine the factors associated with the use of anticoagulants first and then NOAC. Next, a multiple logistic regression analysis was done to determine the independent predictors of anticoagulant indication, and another to evaluate the predictors of NAOC use, utilizing the variables associated with events in the univariate analysis that had $p < 0.10$. A p value <0.05 was considered statistically significant: EpiInfo 2000 software package was used for the analysis.

Ethical considerations

The study was evaluated and approved by the Institutional Ethics Committee.

RESULTS

A total of 484 patients admitted to two coronary care units from January 2015 to December 2018 were included in the study. Fifty-three patients were excluded for presenting CHA_2DS_2-Vasc score = 0, 14 women for having CHA_2DS_2-Vasc score = 1 and 12 patients because they died during hospitalization. Finally, 405 patients were analyzed. Median age was 76 years (IQR 25%-75%: 69-83), 46% were women, 76% hypertensive, 25% diabetic, 10% with history of stroke, 3% with history of bleeding and 30% with history of AF/AFl. The median population CHA_2DS_2-Vasc score was 3 (2-4) and median HAS-BLED score was 2 (1-2). A rhythm control strategy was used in 66% of cases and 68.4% was in sinus rhythm at discharge.

Seventy-two percent of patients received anticoagulant therapy at discharge and 28% had no anticoagulant treatment. Table 1 shows patient characteristics of those receiving anticoagulation compared with those that did not receive it.

Patients who were anticoagulated at discharge were younger, with lower history of AF/AFl (37% vs. 16%, $p<0.001$), diabetes (27.99 vs. 16.96, $p=0.01$) and bleeding (0.68 vs. 8.93, $p<0.001$). Among the variables included in the clinical model to perform the univariate analysis (age >75 years, hypertension, diabetes, history of AF/AFl and history of prior bleeding), only diabetes [OR 2.12 (95% CI 0.95-3.27); $p=0.01$], history of previous AF/AFl [OR 2.83 (95% CI 1.25-4.41); $p=0.0004$) and not having history of prior bleeding [OR 20.97 (95% CI 18.64-23.16); $p=0.007$) were independent predictors of anticoagulation therapy indication at discharge

Among anticoagulated patients at discharge, 2.3% received enoxaparin, 63.5% NOAC and 34.2% vitamin K antagonists. Table 2 shows patient characteristics according to the type of oral anticoagulation therapy at discharge.

The type of NOAC indicated was apixaban in 78.5% of cases, rivaroxaban in 16% and dabigatran in 5.4%. Patients receiving NOAC therapy were younger (74 vs.80 years, $p<0.001$), had lower history of stroke (5.9% vs. 20%, $p<0.01$), coronary heart disease (9.14% vs. 22%, $p=0.022$), chronic kidney failure (2.15% vs. 14%, $p<0.01$), lower median CHA2DS2-Vasc score (3 vs.4, $p<0.01$) and median HAS-BLED score (1 vs.2, $p<0.01$) and more patients were in sinus rhythm at discharge (75.28% vs. 53%, $p<0.001$). In the multivariate analysis, including age >75 years, history of stroke, median CHA_2DS_2-Vasc and HAS-BLED scores, not having chronic kidney failure and sinus rhythm at discharge, only a lower CHA_2DS_2-Vasc score (OR 0.72, 95% CI 0.56-0.94), not having kidney failure [OR 0.19, (95% CI 0.10-0.18); $p<0.01$] and being in sinus rhythm at discharge [OR 2.17 (95% CI 0.95-3.39); $p<0.001$] preserved their independent predictive capacity

Median follow-up of patients discharged with NOAC therapy (n=186) was 14 (8-23) months. During this period 8 patients died and 13 were lost to follow-up. Among the 165 followed-up patients, 55.75% remained in treatment at one year, 22.69% had discontinued treatment (median time to discontinuation: 2 months (IQR 25%-75% 1-4.5 months) and 14.54% had switched to acenocoumarol (median time to

Table 1. Patient characteristics according to the use or not of anticoagulation at discharge. Univariate analysis model.

	AC N: 293 (%)	No AC N: 112 (%)	p
Age (median)	76 (68-82)	78 (69-88)	0.052
Age>75 years	154 (52.56)	64 (57.4)	0.23
Female gender	134 (45.73)	53 (47.32)	0.42
HTN	224 (76.45)	85 (75.89)	0.50
DBT	82 (27.99)	19 (16.96)	0.01
Previous stroke	31 (10.62)	8.93 (10)	0.38
History of EF <30%	13 (4.44)	1 (0.89)	0.06
History of Cardiovascular disease	39 (13.31)	14 (12.5)	0.48
History of atrial fibrillation	104 (35.49)	19 (16.96)	<0.001
Chronic kidney failure	18 (6.14)	9 (8.04)	0.31
CHA2DS2-Vasc score (median)	3 (2-4)	3 (2-4)	0.14
Rhythm control	197(67.24)	71 (63.39)	0.26
Discharge in SR	197 (67.24)	79 (70.54)	0.30
HAS-BLED (median)	2 (1-2)	2(1-2)	0.68
History of bleeding	2 (0.68)	10 (8.93)	<0.001

AC: Anticoagulation. HTN: Hypertension. DBT: Diabetes. EF: Ejection fraction. SR: Sinus rhythm.

Table 2. Patient characteristics according to the type of oral anticoagulant used.

	NOAC N: 186 (%)	Vitamin K antagonists N: 100(%)	p
Age (median)	74 (66-81)	80 (72-84)	<0.01
Age>75 years	84 (45.16)	65 (65)	<0.01
Female gender	86 (46.24)	43 (43)	0.34
HTN	136 (62.39)	82 (82)	0.06
DBT	49 (26.34)	30 (30)	0.29
Previous stroke	11 (5.9)	20 (20)	<0.01
History of AF	63 (33.87)	40 (40)	0.18
Chronic kidney disease	4 (2.15)	14 (14)	0.0001
History of coronary heart disease	17 (9.14)	22 (22)	0.002
CHA_2DS_2-Vasc (median)	3 (2-4)	4 (3-5)	<0.01
Rhythm control	141(75.81)	53 (53)	<0.001
Discharge in SR	140 (75.27)	53 (53)	<0.001
HAS-BLED (median)	1 (1-2)	2 (2-3)	<0.01
History of bleeding	1 (0.54)	1(1)	0.59

NOAC: New oral anticoagulants. HTN: Hypertension. DBT: Diabetes. AF: Atrial fibrillation. SR: Sinus rhythm.

switch: 3.5 months (IQR 25%-75% 2-6 months) since discharge. The treating physician decision was the reason for discontinuation in 87.75% of cases, patient decision in 8.16% and other reasons in 6.12%. In the case of switch from NOAC to acenocoumarol, the reason was due to cost in 41% of cases, treating physician decision in 41% and other reasons in 18%.

DISCUSSION

Atrial fibrillation is the most common sustained arrhythmia and is associated to a fivefold increased risk of major stroke (3) or systemic embolism. Antithrombotic treatment reduces by two-thirds this event (4) and its usefulness is well demonstrated, especially in patients at greater embolic risk. Therefore, national (5) and international (2, 6, 7) guidelines recommend antithrombotic therapy with class Ia indication.

Since 2018, new oral anticoagulants (not dependent on vitamin K) (8) have been added for antithrombotic treatment, and the advantages/disadvantages of their use compared with other therapeutic options poses a clinical challenge. The only available registry of data in our country was performed in 2015, (9) and acenocoumarol was found to be the most recommended anticoagulant agent. In today's world, there is a trend to increase the use of NOAC because they are easy to administer, do not require hematologist's controls and patients anticoagulated with vitamin K antagonists are outside the therapeutic range a large part of the time, despite adequately receiving the medication. (10, 11) The disadvantage of NOAC is their elevated cost and, in some cases, the feeling that no antidotes would be available in case of a severe hemorrhage, though the management of these potential complications is currently well established. (12) Moreover, in large clinical trials comparing different NOAC with the usual therapy with vitamin K antagonists, no increased mortality related with bleeding

was observed in patients receiving NOAC. (13-15)

An interesting finding of our study was that, despite the indication, 30% of patients did not receive anticoagulant therapy at hospital discharge. In this sense, this observation is similar to that found in the CONAREC registry and international registries, such as the GARFIELD-AF (16) registry, where 40% of patients did not receive anticoagulant treatment, or the PINNACLE registry where this increased to 60%. (17) It should be mentioned that in the large international registries mentioned above, including different countries and geographical areas, there is great heterogeneity in the indication of anticoagulation, ranging from 31% to 93% in the GARFIELD-AF registry (16) and 69% to 100% in the ORBIT-AF registry. (18) In addition, as the patients analyzed in the international registries are, in general, ambulatory patients and not recently discharged for arrhythmia, in strict trems, they should not be compared with ours. However, they reflect the reality that not all patients with indication of anticoagulation are receiving treatment and that it is essential to have data disclosing our experience.

In our work, patients with no history of AF received lower prescription of anticoagulant treatment. Nevertheless, current guidelines recommend anticoagulant therapy since the first documented episode, as it is known that patients with recently diagnosed AF are also exposed to considerable risk of stroke, hemorrhage and even, death. Effectively, the GARFIELD-AF registry (19) showed that, even in anticoagulated patients, the one-year incidence of stroke was 1.3%, the rate of major hemorrhage 0.8% and mortality 4.3% (13% of which occurred during the first month). In the same study, during the first 30 days post AF, the rates of stroke and major hemorrhage per 100 person-years was 2.3% (95% CI 1.9-2.8) and 1.5% (95% CI 1.2-1.9), respectively.

The most used anticoagulants after discharge in our population were NOAC. Given the multiple advantages they have, this reality is not surprising and it is even assumed that their use will increase in the next years. (20) In the GLORIA-AF registry (21), NOAC was used in 47.6% of the population and vitamin K antagonists in 32.3% of cases (20.1% did not receive anticoagulation). In the American ORBIT-AF registries, NOAC indication went from 2% in the ORBIT-AF 1 (in 2000) to 71% in the ORBIT-AF 2 (in 2016). Similarly to our work, younger age, lower history of stroke and hemorrhage, preserved kidney function and lower CHA2DS2-Vasc score were predictors of NOAC indication in the ORBIT-AF 2 registry. In their multivariate analysis, factors associated to the use of NOAC were preserved renal function, history of stroke, rhythm control as strategy, treatment by a cardiologist and patient higher educational attainment. (22)

Despite the indisputable benefit of anticoagulation in the prevention of thromboembolism, an elevated percentage of patients have discontinued the medication at one year, ranging between 40% and 60% for vitamin K antagonists in different registries. (23, 24) As NOAC do not require laboratory controls or restrictions in the diet, they could have an advantage in the continuity of therapy, but their cost could also be a barrier for long-.term compliance. The evidence of perseverance in the use of NOAC in the real world is lower than with vitamin K antagonists, outside the scenario of clinical trials demonstrating their usefulness, and it is nil in our country. A substudy of the GLORIA-AF registry (44 countries, 5 regions) describes 76.6% continuity with dabigatran use at one year, 69.2% at two years and 63.4% at the end of follow-up. In the XANTUS study with rivaroxaban, treatment continuity at one year was 80%, (25) but in other experiences it was 60.1%, (26), reflecting the heterogeneity of results according to the population analyzed.

Perhaps the greatest strength of our work is to provide current, proper data of two private centers in Buenos Aires, with patients with social work or prepaid healthcare coverage. In our experience, 3 out of 10 patients with anticoagulant indication are not anticoagulated, NOAC are the most used anticoagulants, 6 out of 10 patients continue NOAC medication at one year, 1 switches to acenocoumarol and 3 discontinue anticoagulant therapy. The most frequent cause of NOAC discontinuation in our population was medical indication, but not cost or adverse effects. Similar results were observed in the GLORIA-AF substudy, where the percentages of discontinuation due to cost were also low: in North America 1%, in Europe 3.1%, in Asia 4%, and in Latin America 0%, (27) while discontinuation due to adverse effects occurred in 1 out of 4 patients.

Limitations

This information stems from the analysis of a population of patients discharged from the coronary care units of private institutions from the Autonomous City of Buenos Aires, and so the type of anticoagulant indication and the one-year adherence may not be the same for other regions or segments of society. It was not the main purpose of this study to explore the reasons why the treating physician decided to discontinue or not indicate anticoagulation in AF, but due to the medical relevance of this topic and the great clinical impact these decisions entail, we consider that it should be treated in future registries

Recommendations of anticoagulation for AF have been continuously changing in the last 10 years, and so new bibliography may dynamically influence medical conduct.

CONCLUSION

In our setting, 2 out of 3 patients receive anticoagulant treatment at discharge. Most of them are currently using NOAC, especially less elderly patients, without kidney failure and lower embolic and bleeding risk. Six out of 10 patients with NOAC indication at discharge continue with treatment, 1 switches to acenocoumarol and 3 abandon treatment at one year.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

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