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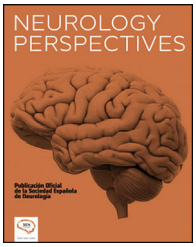

ORIGINAL ARTICLE

Frequency of and factors associated with underdosing of direct oral anticoagulants in patients with ischaemic stroke and atrial fibrillation

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KEYWORDS
Anticoagulants;
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Risk

Abstract
Introduction: Direct oral anticoagulants (DOACs) are the first line of stroke prevention treatment in patients with non-valvular atrial fibrillation (NVAF). However, their inappropriate use is associated with increased risk of stroke, haemorrhagic complications, and mortality. The aim of this study is to analyse the factors associated with the non-prescription of anticoagulants and the underdosing of DOACs.
Methods: We conducted a descriptive study of a prospective registry of patients admitted to a stroke unit due to ischaemic stroke or transient ischaemic attack (TIA) during an 1-year period. We included consecutive patients with history of NVAF with indication for anticoagulant therapy (ACT), according to the CHA_2DS_2-VASc scale. We analysed demographic factors, exposure to vascular risk factors, kidney function, polymedication, and short- and medium-term stroke progression.
Results: Data were obtained from 60 patients admitted due to TIA or ischaemic stroke, with a previous diagnosis of NVAF, of whom 13 (21.7%) were not receiving ACT. Of the remaining 47, 25 (53.2%) were under treatment with DOACs, 21 (44.7%) with vitamin K antagonists, and 1 (2.1%) with heparin. Among patients on DOACs, 8 (32%) were receiving inappropriately low doses, with no differences between drugs.
Age (80.8 vs 74.9 years, $p=.05$) and female sex (75% vs 35.3%, $p=.05$) were associated with underdosing of DOACs. Paroxysmal atrial fibrillation (46.2% vs 14.9%, $p<.005$) and antiplatelet therapy (61.5% vs 8.5%, $p<.005$) were associated with non-prescription of ACT.
Conclusions: Inappropriate use of ACT, including underdosing, is frequent in our setting, occurring in up to one-third of patients admitted due to ischaemic stroke.

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulants; NVAF, non-valvular AF; ACT, anticoagulant therapy; TIA, transient ischaemic attack.

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PALABRAS CLAVE
Anticoagulantes;
Dosis;
Fibrilación auricular;
Ictus;
Riesgo

Resumen
Introducción: Los anticoagulantes orales de acción directa (ACOD) son la primera línea de tratamiento preventivo del ictus en pacientes con fibrilación auricular no valvular (FANv) sin embargo, su uso inapropiado se asocia a mayor riesgo de ictus, complicaciones hemorrágicas y mortalidad. Nuestro objetivo es analizar los factores asociados a la no prescripción de anticoagulación y al uso de dosis baja inapropiada (DBI) en ACOD.
Métodos: Estudio descriptivo de un registro prospectivo de pacientes ingresados por AIT o ictus isquémico en una Unidad de Ictus durante un año. Se incluyeron pacientes consecutivos con antecedentes de FANv con indicación, según escala CHADS-Vasc2, para tratamiento anticoagulante (ACO). Analizamos factores demográficos, exposición a factores de riesgo vascular, función renal, polifarmacia y evolución del ictus a corto y medio plazo.
Resultados: Obtuvimos datos de 60 pacientes ingresados por AIT o ictus isquémico, con diagnóstico previo de FANv, de los cuales 13 (21,7%) no recibían ACO. Del resto (47): 25 (53,2%) tomaban ACOD, 21 (44,7%) con antivitamina K y 1 (2,1%) heparina. Entre los pacientes con ACOD, 8 (32%) recibían DBI, sin diferencias según clase de ACOD.
La edad (80,8 vs 74,9, p = 0,05) y el sexo femenino (75% vs 35,3%, p = 0,05) se asociaron con la prescripción de DBI. La FA paroxística (46,2% vs 14,9%, p < 0,005) y el tratamiento antiagregante (61,5% vs 8,5%, p < 0,005) se asociaron con la no prescripción de ACO.
Conclusiones: El uso inadecuado de la ACO, incluyendo el uso de DBI, es frecuente en nuestro medio pudiendo alcanzar hasta un tercio de los pacientes ingresados por ictus isquémico.

Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia worldwide,[1] with prevalence and incidence rates increasing considerably in line with age. Its prevalence in the adult population in Spain is estimated at 4.4%,[2,3] and is expected to double in the coming decades due to population ageing.[4]

AF significantly increases morbidity and mortality rates,[2] and is associated with a 5-fold increase in the risk of stroke.[1,4] It should also be noted that cardioembolic stroke is the subtype of ischaemic stroke associated with the highest rate of in-hospital mortality, and presents poor short-term prognosis compared to other types of acute ischaemic stroke.[5] Recent studies have identified Bayés syndrome, a cardiac conduction abnormality characterised by interatrial block, as a new risk factor for cardioembolic stroke; this disorder may be involved in events associated with paroxysmal AF.[6] Therefore, early diagnosis and onset of preventive strategies against thromboembolic events through appropriate antithrombotic treatment play a fundamental role in its management.

The first-line treatment in stroke prevention in patients with non-valvular AF (NVAF) is direct oral anticoagulants (DOAC).[4] Four such drugs are currently available: dabigatran (a thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors). These drugs present similar efficacy to vitamin K antagonists (VKA) in preventing thromboembolic events associated with AF, and present a better safety profile.[7,8]

Despite the pharmacological advantages of DOACs over VKAs, it is important when indicating them to bear in mind the need to adjust the dose according to certain patient characteristics, such as age, body weight, kidney function, and potential drug interactions in polymedicated patients.

Recent studies suggest that in real clinical practice, a high percentage of patients are prescribed inappropriate doses.[7,9] In fact, only 63% of patients under treatment with DOACs are estimated to be receiving appropriate doses;[9] incorrect dosage results in increased risk of stroke, ischaemic heart disease, and all-cause mortality and hospitalisation.[7,10]

The objective of this study is to establish the frequency of and the factors associated with non-prescription of anticoagulation or underdosing of DOACs in our setting.

Material and methods

Over a 12-month period, we prospectively registered consecutive patients admitted to our stroke unit with a definitive diagnosis of ischaemic stroke or transient ischaemic attack (TIA) of cardioembolic origin or due to co-existing causes,[11] and with a previous diagnosis of NVAF and indication of anticoagulant therapy (ACT).

Table 1 Summary of the variables analysed.

Demographic variables	Age, sex
Cardiovascular risk factors	Arterial hypertension, dyslipidaemia, diabetes mellitus, smoking, paroxysmal atrial fibrillation, history of stroke
Other clinical characteristics	Antiplatelet therapy, history of stroke, dementia, glomerular filtration rate
Progression during hospitalisation	National Institutes of Health Stroke Scale (NIHSS) score at admission and at discharge, reperfusion treatment (mechanical thrombectomy), haemorrhagic transformation, modified Rankin Scale (mRS) score at discharge, functional independence (mRS of 0–2), in-hospital mortality
Progression at 90 days	Modified Rankin Scale score, functional independence (mRS of 0–2), mortality

Diagnosis of ischaemic stroke and TIA was defined as a qualitative or quantitative alteration in blood supply to the brain, resulting in neurological deficits lasting over 24 h and tissue necrosis (stroke) or a brief episode of neurological dysfunction without evidence of infarction on neuroimaging studies (TIA).[11]

Indication of ACT was established according to the recommendations issued in the latest guidelines for the diagnosis and therapeutic management of AF.[1]

Patients were classified according to the dose of oral anticoagulants prior to admission, as either patients receiving appropriate low doses of DOAC (reduced dose of the drug adjusted for body weight, age, kidney function, and/or potential for drug interactions) or patients receiving inappropriately low doses due to the lack of clinical conditions justifying the reduced dose. We also identified patients who were not receiving any type of ACT.

The main objective of the study was to analyse the factors associated with non-prescription of ACT and underdosing of DOAC. As secondary objectives, we evaluated clinical progression during hospitalisation and at 90 days.

Table 1 summarises the variables analysed.

Statistical analysis included a descriptive study of the main characteristics of patients from both groups; these data are expressed as frequencies and measures of central tendency and dispersion. Quantitative variables were tested for normal distribution using the Kolmogorov–Smirnov test. Qualitative variables are expressed as frequencies and percentages, whereas quantitative variables are expressed as mean and standard deviation or as median and the first and third quartiles (Q_1–Q_3), as appropriate. We conducted a bivariate analysis with hypothesis testing, comparing frequencies when both variables were qualitative (chi-square, Fisher exact test), and comparing means and difference of means when one variable was quantitative (*t* test and such non-parametric tests as the Mann–Whitney *U* test for non-normally distributed variables). Statistical significance for the association between 2 variables was set at $p < .05$. Data were analysed using the STATA 14 statistics and data analysis software.

The study complied with the requirements of the Declaration of Helsinki, as well as the applicable Spanish legislation on the performance of observational studies. Data were pooled for the analysis and dissemination of findings. Individual patient data were kept confidential at all times. The documents and database generated during the study will be protected from unauthorised use by anyone not involved in the study and will therefore be considered strictly confidential.

Results

Between January and December 2021, a total of 443 patients were admitted to our stroke unit, with 385 (86.9%) presenting ischaemic stroke or TIA. Sixty patients (15.6%) presented history of NVAF with indication for ACT; 13 of these (21.7%) were not receiving any kind of anticoagulant.

Table 2 shows the baseline characteristics of the ACT and no-ACT groups. The 2 groups showed no significant

Table 2 Demographic characteristics, exposure to cardiovascular risk factors, and other clinical characteristics in patients with known atrial fibrillation, receiving and not receiving anticoagulant therapy.

	ACT (*n*=47)	No ACT (*n*=13)	*p*
Age in years, mean (SD)	78.3 (1.3)	79.6 (2.5)	.63
Women, *n* (%)	24 (51.1)	5 (38.5)	.31
Arterial hypertension, *n* (%)	42 (89.4)	10 (76.9)	.23
Dyslipidaemia, *n* (%)	21 (44.7)	7 (53.9)	.39
Diabetes mellitus, *n* (%)	16 (34.1)	3 (23.1)	.35
Smoking, *n* (%)	5 (10.6)	1 (7.7)	.61
Paroxysmal AF, *n* (%)	7 (14.9)	6 (46.2)	.001
Antiplatelet drugs, *n* (%)	4 (8.5)	8 (61.5)	<.001
Prior stroke, *n* (%)	17 (36.2)	3 (23.1)	.38
Cognitive impairment, *n* (%)	0 (0)	0 (0)	
GFR, mean (SD)	71.2 (3.4)	74.9 (9.9)	.65

ACT: anticoagulant therapy; AF: atrial fibrillation; GFR: glomerular filtration rate; SD: standard deviation.

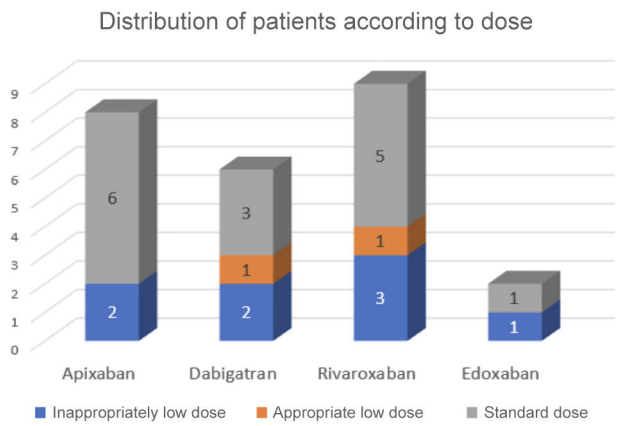

Fig. 1 Distribution of doses for each direct oral anticoagulant.

differences in demographic variables, cardiovascular risk factors, or clinical characteristics. However, the no-ACT group did present a significantly higher level of antiplatelet use.

Of the 47 patients receiving ACT, 25 (53.2%) were receiving a DOAC. Eight (32%) of these were receiving an inappropriately low dose. Fig. 1 shows the prescribed doses of each drug.

Table 3 shows patients' baseline characteristics, according to the DOAC doses received. No statistically significant differences were observed in the variables analysed. However, a female predominance and older mean age were observed in the underdosing group. Furthermore, we observed a trend towards lower prevalence of underdosing among patients with history of stroke.

Patients receiving inappropriately low doses of DOACs scored higher on the NIHSS at admission, and presented poorer clinical recovery (change in NIHSS score between admission and discharge). No cases of haemorrhagic transformation of stroke were observed in the underdosing group, compared to 2 asymptomatic cases (11.8%) in the appropriate doses group. Two patients (11.8%) in the appropriate doses group died during hospitalisation (due to non-neurological causes: complications of a respiratory infection in both); no patient in the underdosing group died.

Twenty-five patients were evaluated at 90 days (2 losses to follow-up); the underdosing group showed a lower rate of functional independence (mRS of 0–2) and a higher mortality rate. Two patients in the underdosing group died due to neurological causes (recurrent stroke) within 90 days; another patient in the appropriate doses group died due to unknown causes.

The results for in-hospital and 90-day progression are summarised in Tables 4 and 5, respectively.

Discussion

Our results show that, despite indication of ACT, slightly more than one in 5 patients (21.7%) admitted due to ischaemic stroke or TIA with history of NVAF were not receiving ACT; of those who were receiving DOACs, 32% were prescribed inappropriately low doses. This is a higher percentage than that reported in other studies, which estimate that 25% of cases worldwide receive inappropriately low doses of DOACs.[12]

According to recent publications, the factors most consistently associated with more frequent underdosing include female sex, age > 65 years, mild kidney failure (creatinine clearance ≤ 50 mL/min), arterial hypertension,

Table 3 Demographic characteristics, exposure to cardiovascular risk factors, and other clinical characteristics in patients with known atrial fibrillation, receiving appropriate and inappropriate doses of direct oral anticoagulants.

	Appropriate doses	Underdosing	*p*
	n = 17	*n* = 8	
Age in years, mean (SD)	74.9 (2.1)	80.8 (1.1)	.06
Women, *n* (%)	6 (35.3)	6 (75)	.06
Arterial hypertension, *n* (%)	14 (82.4)	8 (100)	.29
Dyslipidaemia, *n* (%)	8 (47.1)	2 (25)	.27
Diabetes mellitus, *n* (%)	9 (52.9)	2 (25)	.19
Smoking, *n* (%)	1 (5.9)	0 (0)	.68
Paroxysmal AF, *n* (%)	3 (17.7)	1 (12.5)	.62
Antiplatelet drugs, *n* (%)	1 (5.9)	1 (12.5)	.55
Prior stroke, *n* (%)	7 (41.2)	1 (12.5)	.17
Cognitive impairment, *n* (%)	0 (0)	0 (0)	
GFR, mean (SD)	68.6 (6.7)	69 (10.3)	.65

AF: atrial fibrillation; GFR: glomerular filtration rate; SD: standard deviation.

Table 4 In-hospital progression of patients with known atrial fibrillation and receiving appropriate and inappropriate doses of direct oral anticoagulants.

	Total	Appropriate doses	Underdosing	*p*
		n=17	*n*=8	
NIHSS at admission, median (Q_1–Q_3)	12 (5–17)	10 (6–16)	17 (1.5–20.5)	.40
NIHSS at discharge, median (Q_1–Q_3)	5.5 (1–13)	4 (0.5–10)	6.5 (1–18)	.89
Change in NIHSS, median (Q_1–Q_3)	3 (0–9)	5 (0–9)	0.5 (0–6)	.21
Reperfusion treatment, *n* (%)	6 (24)	6 (35.3)	2 (25)	.44
Primary mechanical thrombectomy				
Haemorrhagic transformation, *n* (%) (asymptomatic)	4 (16)	4 (23.5)	0 (0)	.06
mRS at discharge, median (Q_1–Q_3)	2 (1–5)	2 (1–4)	2.5 (1.5–5)	.99
Functional independence, *n* (%)	13 (52)	9 (50)	4 (50)	.89
In-hospital mortality, *n* (%)	2 (8)	2 (11.8)	0 (0)	.20

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; Q_1–Q_3; quartiles 1 and 3.

non-white ethnicity, history of acute coronary syndrome, previous stroke, diabetes, and concomitant treatment with antiplatelet drugs. In our sample, underdosing was more frequent among women and older patients, who may be considered more frail and, therefore, more vulnerable to haemorrhagic complications. However, we observed a lower rate of underdosing of DOACs in patients with history of stroke, probably due to greater concern about thromboembolic risk among patients who had presented ischaemic events.

In the ESPARTA study,[13] whose main objective was to assess compliance with the recommendations of the Therapeutic Positioning Report on oral anticoagulation in patients with NVAF attended at internal medicine units in Spain, patients receiving DOACs displayed better compliance with the recommendations than those receiving VKAs (57% vs 34.4%). The most frequent cause of non-compliance was the use of reduced doses despite the standard dose being recommended; this may be explained by the considerable concerns about haemorrhagic risk. However, DOACs have been demonstrated to be safer than VKAs, according to the results of a meta-analysis comparing the efficacy and safety of both drug classes, which reported a 10% reduction in all-cause mortality and a 52% reduction in intracranial haemorrhage in patients receiving DOACs.[8,14]

Furthermore, some studies report that underdosing is more frequent among patients with higher CHA_2DS_2-VASc scores, which suggests that the patients with greatest thromboembolic risk are those receiving insufficient doses of DOACs.[4,7,12] Underdosing has also been shown to significantly increase the risk of adverse reactions.[9,10] Specifically, patients receiving inappropriately low doses of DOACs present higher mortality rates and greater frequency of thromboembolic complications, with no beneficial effect in the reduction of haemorrhagic complications.[15,16] In our study, both short- and medium-term follow-up (90 days) of patients receiving inappropriately low doses of DOACs showed a trend towards poorer functional outcomes and higher mortality rates, although the rate of haemorrhagic transformation was lower among these patients during the follow-up period.

A recent meta-analysis evaluated the impact of underdosing of DOACs, finding that insufficient doses of these drugs had a null effect on haemorrhagic risk, compared to recommended doses (hazard ratio of 1.04; 95% confidence interval, 0.90–1.19; p=.625).[7] In other words, inappropriately low doses of these drugs do not reduce haemorrhagic risk, and therefore offer no safety benefit,[7] even in elderly and frail patients, in whom the greatest clinical benefit is achieved with the standard dose of the drug.[17,18]

The impact of underdosing may differ according to the specific drug and dose used, as reduced doses of rivaroxaban and dabigatran are approximately 25% lower than the standard dose, compared to 50% for apixaban and edoxaban. However, limited evidence is available and there is a need for more studies evaluating the impact of underdosing for different types of anticoagulants.[19]

Generally speaking, to reduce any kind of complications associated with DOAC treatment, regardless of the dose

Table 5 Ninety-day progression of patients with known atrial fibrillation at the time of admission due to ischaemic stroke or transient ischaemic attack and receiving appropriate or inappropriate doses of direct oral anticoagulants.

	Total	Appropriate doses	Underdosing
	n=25	*n*=17	*n*=6 [a]
mRS, median (Q_1–Q_3)	2 (0–4)	2 (0–3)	2 (0–6)
Functional independence, *n* (%)	14 (56)	10 (58.9)	4 (66.7)
Mortality, *n* (%)	4 (16)	2 (11.8)	2 (33.3)

[a] Two patients were lost to follow-up. mRS: modified Rankin Scale; Q_1–Q_3: quartiles 1 and 3.

administered, it seems reasonable to monitor kidney function, as well as any other modifiable risk factors associated with haemorrhagic risk, during the follow-up of these patients.[4,17,19,20]

The limitations of the study include its small sample size, which prevents us from achieving sufficient statistical power for some of the variables studied, as well as the short follow-up period. Furthermore, doses of DOACs were analysed at the time of the thromboembolic event, and not at the time of prescription; therefore, it is unclear whether doses were modified as a result of changes in patients' clinical characteristics; this underscores the need for proper follow-up.

Conclusion

Underdosing of DOACs in patients with known NVAF and presenting thromboembolic stroke is common in our setting. This phenomenon is more frequent among women and elderly patients, and is associated with poorer clinical outcomes; patients receiving appropriate doses more frequently presented haemorrhagic complications, though these were asymptomatic. The available evidence suggests that non-recommended reduction of DOAC dose offers no benefits in terms of treatment safety and is associated with increased mortality, as observed in our sample.

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Informed consent

This study does not include any data that could reveal any patient's identity.

Ethical considerations

This study complies with all relevant ethical standards.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2024.100160.

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