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


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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 CHA²DS²-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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Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia worldwide, with prevalence and incidence rates increasing considerably in line with age. Its prevalence in the adult population in Spain is estimated at 4.4%, and is expected to double in the coming decades due to population ageing. AF significantly increases morbidity and mortality rates, and is associated with a 5-fold increase in the risk of stroke. 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. 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 AF, and presents a better safety profile.

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. In fact, only 63% of patients under treatment with DOACs are estimated to be receiving appropriate doses; incorrect dosage results in increased risk of stroke, ischaemic heart disease, and all-cause mortality and hospitalisation. 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, and with a previous diagnosis of NVAF and indication of anticoagulant therapy (ACT).
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).\(^1\)

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.

### Table 1

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Cardiovascular risk factors</th>
<th>Other clinical characteristics</th>
<th>Progression during hospitalisation</th>
<th>Progression at 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, sex</td>
<td>Arterial hypertension, dyslipidaemia, diabetes mellitus, smoking, paroxysmal atrial fibrillation, history of stroke</td>
<td>Antiplatelet therapy, history of stroke, dementia, glomerular filtration rate</td>
<td>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</td>
<td>Modified Rankin Scale score, functional independence (mRS of 0–2), mortality</td>
</tr>
</tbody>
</table>

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 differences.

### Table 2

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

ACT: anticoagulant therapy; AF: atrial fibrillation; GFR: glomerular filtration rate; SD: standard deviation.
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,
whose main objective was to
9
Underdosing has also been shown to
even in elderly and frail patients, in whom the
In our
In other
of DOACs.
which suggests that the patients with greatest
scores, which suggests that the patients with greatest
thromboembolic risk are those receiving insufficient doses
of both drug classes, which reported a 10% reduction in all-
results of a meta-analysis comparing the efficacy and safety
been demonstrated to be safer than VKAs, according to the
concerns about haemorrhagic risk. However, DOACs have
recommended; this may be explained by the considerable
use of reduced doses despite the standard dose being
34.4%). The most frequent cause of non-compliance was the
patients receiving DOACs displayed better compliance with
the recommendations than those receiving VKAs (57% vs
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
despite a null effect on haemorrhagic complications. In
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.
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.
Generally speaking, to reduce any kind of complications
associated with DOAC treatment, regardless of the dose
Table 4  In-hospital progression of patients with known atrial fibrillation and receiving appropriate and inappropriate doses of direct oral anticoagulants.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Appropriate doses</th>
<th>Underdosing</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=17</td>
<td>n=8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS at admission, median (Q1–Q3)</td>
<td>12 (5–17)</td>
<td>10 (6–16)</td>
<td>17 (1.5–20.5)</td>
<td>.40</td>
</tr>
<tr>
<td>NIHSS at discharge, median (Q1–Q3)</td>
<td>5.5 (1–13)</td>
<td>4 (0.5–10)</td>
<td>6.5 (1–18)</td>
<td>.89</td>
</tr>
<tr>
<td>Change in NIHSS, median (Q1–Q3)</td>
<td>3 (0–9)</td>
<td>5 (0–9)</td>
<td>0.5 (0–6)</td>
<td>.21</td>
</tr>
<tr>
<td>Reperfusion treatment, n (%)</td>
<td>6 (24)</td>
<td>6 (35.3)</td>
<td>2 (25)</td>
<td>.44</td>
</tr>
<tr>
<td>Primary mechanical thrombectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic transformation, n (%)</td>
<td>4 (16)</td>
<td>4 (23.5)</td>
<td>0 (0)</td>
<td>.06</td>
</tr>
<tr>
<td>(asymptomatic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS at discharge, median (Q1–Q3)</td>
<td>2 (1–5)</td>
<td>2 (1–4)</td>
<td>2.5 (1.5–5)</td>
<td>.99</td>
</tr>
<tr>
<td>Functional independence, n (%)</td>
<td>13 (52)</td>
<td>9 (50)</td>
<td>4 (50)</td>
<td>.89</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>2 (8)</td>
<td>2 (11.8)</td>
<td>0 (0)</td>
<td>.20</td>
</tr>
</tbody>
</table>

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; Q1–Q3: quartiles 1 and 3.

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.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Appropriate doses</th>
<th>Underdosing</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=25</td>
<td>n=17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS, median (Q1–Q3)</td>
<td>2 (0–4)</td>
<td>2 (0–3)</td>
<td>2 (0–6)</td>
<td>.08</td>
</tr>
<tr>
<td>Functional independence, n (%)</td>
<td>14 (56)</td>
<td>10 (58.9)</td>
<td>4 (66.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>4 (16)</td>
<td>2 (11.8)</td>
<td>2 (33.3)</td>
<td>.20</td>
</tr>
</tbody>
</table>

a Two patients were lost to follow-up. mRS: modified Rankin Scale; Q1–Q3: 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.\textsuperscript{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.

**Funding**

This study has received no funding of any kind.

**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.

**References**


