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Recurrent stroke despite correct anticoagulation therapy with DOACs: Analysis of the real-life therapeutic approach

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ABSTRACT

Introduction and objectives: Recurrent strokes persist despite the use of guideline-recommended direct oral anticoagulants (DOACs). There is a scarcity of data concerning the current and optimal practices following a recurrent stroke while on DOACs. Consequently, our aim was to identify factors associated with this residual risk and to discern the current practice patterns among cardiologists and neurologists.

Methods: All consecutive patients with an acute cerebrovascular accident of any type and a diagnosis of atrial fibrillation (AF) were retrospectively screened at our stroke center. We gathered demographic information, clinical risk scores (CHA_2DS_2-VASc and HAS-BLED), echocardiographic and laboratory findings, risk factors, the modified Rankin score, and information about the treatment modality. DOAC usage was classified as either inappropriate (due to self-reported non-adherence and/or incorrect DOAC dosage) or appropriate.

Results: A total of 77 patients with stroke despite treatment with DOACs were included in the analysis. Of these, 28 (36%) had received inappropriate treatment (20 of them due to inadequate dosing). These patients tended to be older ($P = .06$) and had lower creatinine levels than the group receiving appropriate DOACs (0.9 vs 1; $P = .01$). At hospital discharge following the index stroke, various anticoagulants were administered to 75 patients (enoxaparin, n = 5; warfarin, n = 10; DOAC, n = 60). Two patients died and 20 patients were given antiplatelet therapy in addition to anticoagulants. The preferred DOACs after stroke were apixaban ($n = 27$), followed by rivaroxaban ($n = 16$), dabigatran ($n = 14$) and edoxaban ($n = 3$).

Conclusions: There is no standardized model or consensus among physicians regarding anticoagulant management. Despite the intended use of the drugs, strokes continue to occur in some patients. The 25% of strokes are related to inadequate dosage.

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Ictus recurrente a pesar del tratamiento anticoagulante correcto con ACOD: análisis del abordaje terapéutico en la vida real

Palabras clave:
Datos del mundo real
Ictus recurrente
Anticoagulantes orales no antagonistas de la vitamina K
Anticoagulantes orales directos

RESUMEN

Introducción y objetivos: A pesar de un tratamiento anticoagulante correcto con anticoagulantes orales de acción directa (ACOD), puede existir cierto riesgo residual, y algunos pacientes sufren ictus recurrente. En la literatura existen pocos datos acerca de cuál es la forma óptima de tratar a estos pacientes, y de cuáles son las estrategias más utilizadas en la práctica clínica habitual. Nuestro objetivo fue identificar los factores asociados a este riesgo residual, y analizar los patrones de tratamiento adoptados por cardiólogos y neurólogos.

Métodos: Se incluyó de forma retrospectiva a todos los pacientes consecutivos con fibrilación auricular (FA) que sufrieron un accidente cerebrovascular agudo de cualquier tipo en nuestro centro de ictus. Se recogió la información demográfica, las puntuaciones de riesgo CHA_2DS_2-VASc y HAS-BLED, los hallazgos ecocardiográficos y de laboratorio, los factores de riesgo, la puntuación de Rankin modificada y la información sobre la modalidad del tratamiento del ictus en fase aguda. El uso de los ACOD se clasificó como inapropiado (por falta de adherencia autodeclarada o por dosificación incorrecta de los ACOD) o apropiado.

Resultados: Se incluyó en el análisis a 77 pacientes con ictus a pesar de tratamiento con ACOD. De ellos, 28 (36%) recibieron un tratamiento inapropiado (20 de ellos por dosificación inadecuada). Estos pacientes tendían a ser de mayor edad (p = 0,06) y presentaban unos niveles de creatinina inferiores a los del grupo que recibió ACOD apropiado (0,9 frente a 1; p = 0,01). Al alta hospitalaria tras el ictus índice, se administró tratamiento anticoagulante a 75 pacientes (enoxaparina, n = 5; warfarina, n = 10; ACOD, n = 60). Dos pacientes fallecieron y en 20 se añadió tratamiento antiagregante plaquetario a la medicación anticoagulante. El ACOD preferido tras un ictus fue apixabán (n = 27), seguido de rivaroxabán (n = 16), dabigatrán (n = 14) y edoxabán (n = 3).

Conclusiones: No existe un modelo estandarizado ni consenso entre los médicos respecto al tratamiento con ACOD tras un ictus. A pesar de un uso correcto de estos fármacos, siguen produciéndose accidentes cerebrovasculares en algunos pacientes. Un 25% de los ictus guardan relación con una dosificación inadecuada.

Introduction

Atrial fibrillation (AF), which accounts for 50% of all cardioembolic strokes, is increasing in parallel with the aging of the population.[1] Currently, the most effective medical therapy for the prevention of AF-related stroke is direct oral anticoagulants (DOAC), which are similar or superior to vitamin K antagonists (VKA) in efficacy and mostly superior in terms of safety.[2] However, despite receiving the guideline-recommended dose-adjusted DOAC therapy, some patients appear to have a residual risk of stroke that is even higher than in patients who are anticoagulation-naïve, which is around 1%–3% both in landmark trials and real-world studies.[3–5]

Uncertainties still exist regarding the prevalence and cause of stroke in patients with nonvalvular AF despite DOAC therapy and how to minimize this residual risk. Owing to a lack of sufficient data, even the most recent guidelines have not made firm recommendations on this matter.[6]

Our objective was to define the current real-world practices after stroke despite treatment with DOACs among cardiologists and neurologists and to explore the role of both human errors and other possible reasons behind this phenomenon.

Methods

Study population, study design, and inclusion or exclusion criteria

All consecutive patients with an acute cerebrovascular accident of any type (ICD-10 codes: G46/I61/I63/I64/I66/I67/I68) and a concurrent diagnosis of AF (all types included) between 2019 and 2022 were retrospectively screened at a comprehensive stroke center. After the generation of the eligible patient list from the hospital admission database, the type of cerebrovascular accident was confirmed by a neurologist by reviewing the electronic health record on a case-by-case analysis. In the case of multiple events in the same patient, only the most recent event was recorded.

Patients with hemorrhagic stroke, those treated with agents other than DOACs (ie, warfarin, low-molecular-weight

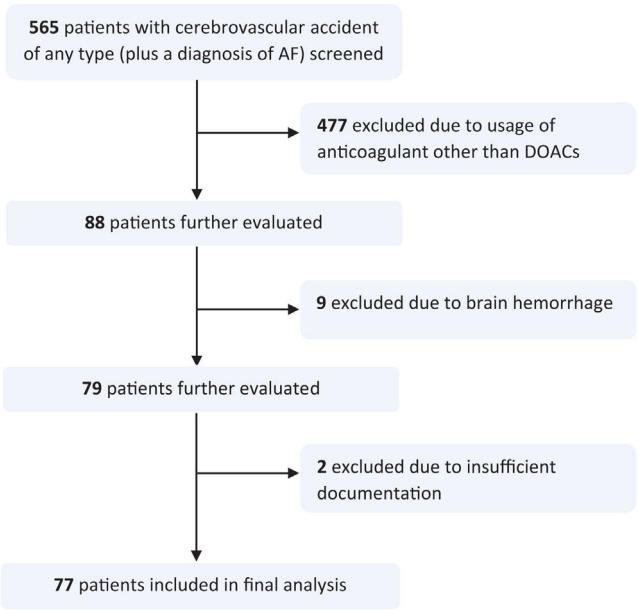

Fig. 1 – Flowchart of the study. AF, atrial fibrillation; DOACs, direct oral anticoagulants.

heparin, and antiplatelet only), and those with incomplete data (either before or after the event) were excluded (refer to the study flowchart in Fig. 1). The inclusion criteria for the final data analysis were as follows: age ≥ 18 years, nonvalvular AF of any duration, and being under treatment with a DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) at the time of the index stroke onset.

The criteria for the application of percutaneous left atrial appendage (LAA) closure in our center encompassed the existence of a contraindication to long-term anticoagulation and the recurrence of stroke despite suitable anticoagulation. However, for those experiencing recurrent strokes despite DOACs, there was no standardized protocol, and the course of action was left to the discretion of the individual physician.

Approval was obtained from the local ethics committee of the Tepecik Training and Research Hospital (İzmir, Turkey) and informed consent was waived because of the retrospective nature of the study (approval number: 2023/01-35).

Variables

In addition to demographic and medication data, clinical risk scores (CHA_2DS_2-VASc and HAS-BLED), echocardiographic parameters (left atrial diameter and left ventricular ejection fraction), laboratory findings (creatinine, lipid profile, and glycated hemoglobin [HbA1c]), risk factors [prior stroke/transient ischemic attack, hypertension, diabetes, atherosclerosis, and hyperlipidemia], the modified Rankin score (mRS) for the evaluation of stroke severity at admission, and acute stroke treatment modality (endovascular or medical only) were collected. The left atrial diameter was obtained from the anteroposterior direction in the parasternal long-axis view. Parent artery disease refers to significant stenosis of the internal carotid artery, middle cerebral artery, and vertebrobasilar system.

All patients underwent pre-contrast computed tomography, and almost all underwent diffusion magnetic resonance imaging. In all patients, standardized transthoracic echocardiography and carotid/vertebral Doppler testing for cardiovascular causes of stroke were performed within 7 days of stroke onset. In selected cases with suspected vascular etiology of stroke, brain computed tomography angiography was also performed.

DOAC usage was categorized as inappropriate if any of the following conditions were present: self-reported non-adherence, or a DOACs dosage that was erroneously low or high according to the most recent drug label (see supplementary data for detailed dosage information based on the manufacturer's labeling). It was considered appropriate otherwise. This categorization was done to eliminate the potential confounding effect of human error, which is quite common with DOAC use.[7]

Statistical analyses

Clinical and demographic characteristics are presented as mean ± standard deviation or median with interquartile range for continuous variables, and frequency (percent) for categorical variables. The normality of the variables was determined using the Kolmogorov–Smirnov test with a Lilliefors significance correction and the Shapiro–Wilk test. Comparisons between patients using appropriate and inappropriate DOACs were made using Fisher's exact test for categorical variables and unpaired *t*-test or Mann–Whitney *U* test for continuous variables. A 2-tailed $P < .05$ was considered statistically significant. Data analysis was conducted using the IBM SPSS Statistics software (version 26; IBM Corporation, United States). This study complies with the Declaration of Helsinki (2013).

Results

Of the 565 patients screened, 77 patients (13.6%) with ischemic stroke/transient ischemic attack while on DOACs were identified for the final analysis (Fig. 1). The baseline characteristics are shown in Table 1. Patients in the inappropriate group, which includes non-compliant and inappropriately dosed patients, tended to be older, although the difference was not statistically significant ($P = .06$). There were no statistically significant differences between the 2 groups in terms of bleeding risk as assessed by HAS-BLED and comorbidities. Creatinine levels in the inappropriate group were lower than in the appropriate group (0.9 vs 1; $P = .01$). Within the 'inappropriate' DOACs group ($n = 28$), an erroneous dosage was identified in 20 patients, accounting for 71.4% of the group. Of these incorrect dosages, 90% ($n = 18$) were due to underdosing, while the remaining 10% ($n = 2$) were due to overdosing. Apixaban was the most frequently mis-dosed DOACs ($n = 14$; for a comprehensive list of erroneously dosed DOACs, refer to Table 2). The remaining 8 patients, representing 28.6% of the group, exhibited non-compliance with their prescribed DOAC regimen. The primary cause of non-adherence was forgetfulness, with patients often failing to take the medication as prescribed. The subsequent most prevalent reason was apprehension about

Table 1 – Baseline characteristics of the study cohort.

Variable	Total ($n=77$)	Appropriate ($n=49$; 63.6%)	Inappropriate ($n=28$; 36.4%)	P
Demographics				
Age (years)	73.9 ± 8.7	72.5 ± 8.7	76.4 ± 8.2	.06
Female	42 (54.5%)	25 (51%)	17 (6.7%)	.4
Clinical parameters				
CHA_2DS_2-VASc score, Mdn, [IQR]	6 [2]	5 [2]	6 [3]	.4
HAS-BLED score, Mdn, [IQR]	2 [1]	2 [1]	2 [1.2]	.7
Modified Rankin scale, Mdn, [IQR]	2 [3]	1 [2]	3 [4]	.1
Parent artery disease	17 (22%)	9 (18.3%)	8 (28.5%)	.06
Echocardiographic parameters				
LVEF (%), Mdn, [IQR]	55 [10]	55 [10]	55 [10]	.7
Left atrium diameter	43 ± 6.3	42.2 ± 6.9	44.3 ± 5.1	.1
Comorbidities				
Previous stroke	43 (55.8%)	27 (55.1%)	16 (57.1)	1
Hypertension	61 (79.2%)	40 (81.6%)	21 (75%)	.5
Diabetes	34 (44.1%)	22 (44.8%)	12 (42.8%)	1
Atherosclerosis	30 (38.9%)	20 (40.8%)	10 (35.7)	.8
Hyperlipidemia	6 (7.7%)	4 (8.1%)	2 (7.1%)	1
Laboratory				
Creatinine, Mdn, [IQR]	0.9 [0.4]	1 [0.4]	0.9 [0.1]	.01
HbA1c, Mdn, [IQR]	6.4 [1.6]	6.5 [1.5]	5.9 [1.7]	.05
Stroke treatment				
Endovascular	9 (11.6%)	2 (4.1%)	7 (25%)	.01
Medical only	68 (88.4%)	47 (95.9%)	21 (75%)	

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol; IQR, interquartile range; LVEF, left ventricular ejection fraction; Mdn, median.

Table 2 – Numbers of different DOACs used prior to the stroke.

DOACs	Total ($n=77$)	Appropriate ($n=49$; 63.6%)	Inappropriate ($n=28$; 36.4%)
Dabigatran	19	14	5
Rivaroxaban	21	14	7
Apixaban	25	11	14
Edoxaban	12	10	2

DOACs, direct oral anticoagulants. The medicines are listed in the order of their release date.

severe bleeding following a minor event, such as transient epistaxis. No significant difference was observed in compliance across the various DOACs.

A total of 5 patients were already taking add-on antiplatelet treatment before the index event (aspirin, $n=4$; clopidogrel, $n=1$), and this number increased to 20 patients after the index stroke (aspirin, $n=17$; clopidogrel, $n=6$). Two patients passed away during the index hospitalization, 9 patients (11.6%) underwent endovascular thrombectomy, 68 (88.4%) received only medical therapy, and none received thrombolytic therapy. The choice of endovascular therapy as a treatment was significantly higher in the appropriate DOACs group than in the inappropriate group (95.9% vs 75%; $P=.01$). Furthermore, as a non-pharmacological preventive measure, four patients underwent percutaneous closure of the LAA after the stroke.

At hospital discharge following the index stroke, anticoagulants were administered to 75 patients (enoxaparin, $n=5$; warfarin, $n=10$; DOACs, $n=60$; Fig. 2). The most preferred anticoagulant administered after a recurrent stroke was apixaban ($n=27$), followed by rivaroxaban ($n=16$), and dabigatran ($n=14$). Edoxaban was given to 3 patients. All changes in anticoagulant prescriptions are depicted in a Sankey diagram (Fig. 3).

The presence of parent artery disease was found to have a positive correlation with mRSs in the inappropriate group ($U=18$; $P=.001$); however, this correlation was not observed when all patients were included ($U=362$; $P=.06$).

Discussion

This study investigated the role of prescribed DOACs in patients who suffered an incident stroke while on therapy. It sought to determine how clinicians manage this unfortunate situation and revealed three major findings: (a) After excluding 28 inappropriately anticoagulated patients, recurrent ischemic stroke occurred in 49 patients despite appropriate anticoagulation with DOACs. (b) A high proportion of patients are still being prescribed off-label doses of DOACs. (c) Warfarin and low-molecular-weight heparin are still being

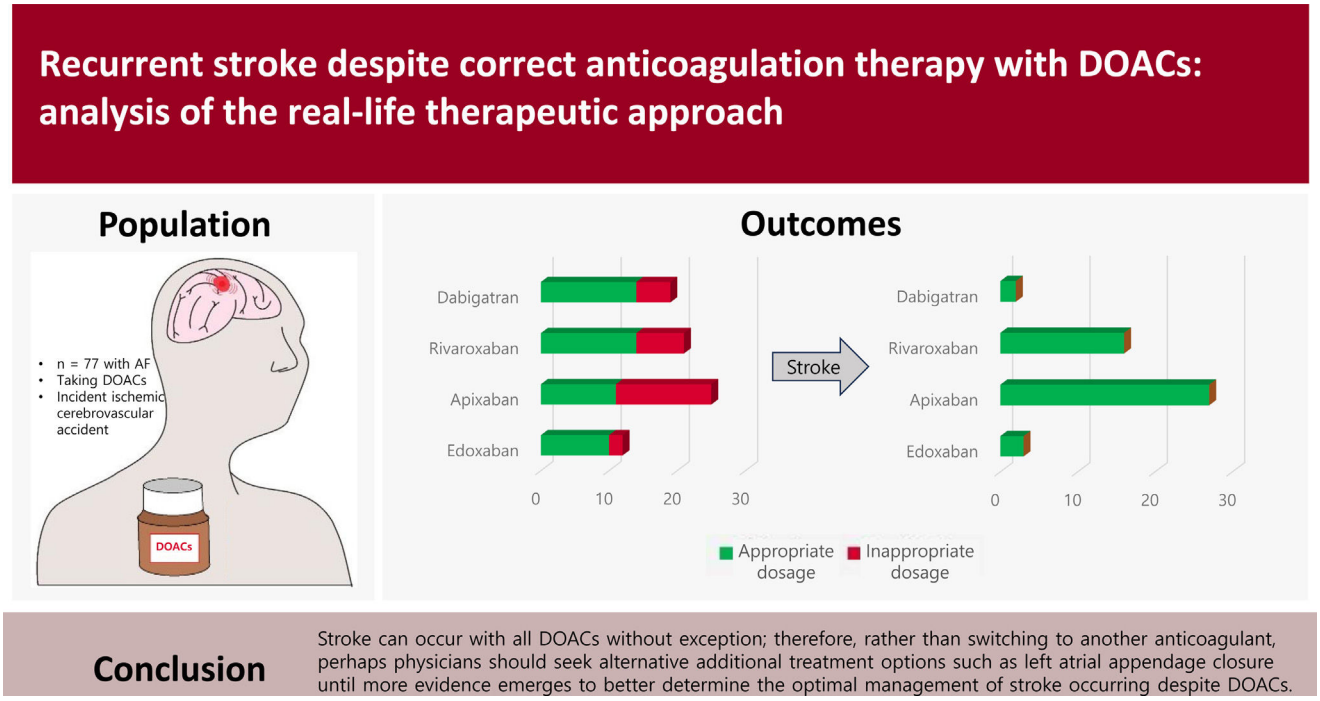

Fig. 2 – Central illustration. Depicting population characteristics and anticoagulant choices before and after stroke. AF, atrial fibrillation; DOACs, direct oral anticoagulants.

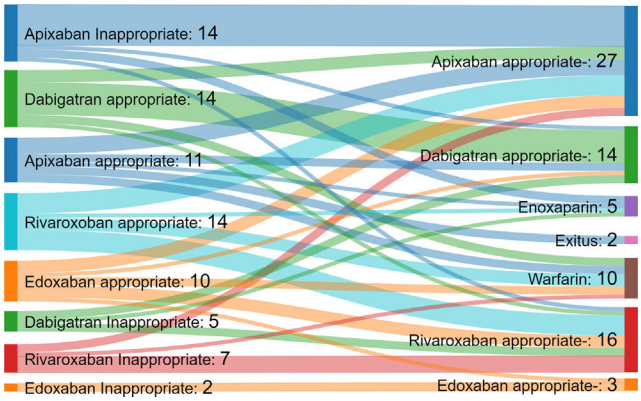

Fig. 3 – Change of oral anticoagulants (the Sankey diagram).

used as substitutes for DOACs after a stroke, despite studies showing better results with DOACs, even after a recurrent stroke.[1,8] Although the study data were derived from a very busy hospital setting in a metropolitan city and are largely representative of the country as a whole, these results should be interpreted with caution as they were obtained from a single center.

We speculated on the reasons and potential solutions for incident stroke in patients already anticoagulated with appropriately dosed DOACs as follows. (a) One possibility is a competing non-cardioembolic stroke mechanism, such as large artery atherosclerosis or small vessel disease. Anticoagulation has not been shown to be superior to antiplatelet agents in these cases and may even increase the risk of hemorrhagic complications. This could be the cause of the index stroke, with AF simply being a bystander. Indeed, in our study, 1 in 5 patients (22%) had some form of parent artery disease. However, as we did not have a control group (ie, patients who did not have a recurrent stroke while on DOACs), no comparison could be made. Furthermore, the findings in previous studies that adding antiplatelet therapy on top of DOACs may not lead to a better outcome or may even cause harm could be simply due to the increased risk of bleeding caused by DOACs themselves.[8,9] Other less common coagulopathies, such as cancer-associated antiphospholipid syndrome, and cardiac pathologies, including endocarditis, left ventricular thrombus, and prosthetic heart valves, may also serve as underlying mechanisms for stroke in patients on DOACs. These conditions could potentially contribute to the incidence of stroke despite appropriate anticoagulation.[8] (b) Previous studies have demonstrated that recurrent ischemic stroke can occur under oral anticoagulation, even in patients with similar CHA_2DS_2-VASc scores, but who have more frequent vascular risk factors such as hypertension, diabetes, and hyperlipidemia. In line with the literature, our study cohort exhibited a high median CHA_2DS_2-VASc score of 6 and a very high prevalence of hypertension (79.2%). These vascular risk factors may have a deleterious effect on vessel walls, potentially reducing the protective effects of DOACs. This could be due to their role as a component of the Virchow triad.[5,9] (c) Despite appropriate dosing as per drug labels, inter-individual variability in the pharmacological efficacy of DOACs, in terms of both pharmacokinetics and pharmacodynamics, as well as potential drug-drug interactions might be contributing factors to the failure in preventing stroke. Although we cannot provide a definitive opinion on this issue due to the unavailability of blood drug levels in our study, we propose that an individ-

ual pharmacogenetic approach could serve as an alternative solution in refractory cases of stroke.

Reflecting on the most current drug prescribing habits, this study showed that inappropriate dosing rates are still high. There are several possible reasons behind this counterintuitive practice, primarily health system barriers and prescription factors. Time constraints may make it difficult for healthcare providers to spend the necessary time with each patient to determine the optimal dose. Furthermore, a lack of motivation to continue medical education after graduation may prevent healthcare providers from keeping up with the latest guidelines and research on DOAC dosing. In addition, prescribing factors such as the prescriber's understanding and concerns about the side effects of treatment may also influence decisions. Interestingly, although there was no significant difference in HAS-BLED scores and patient age between appropriately and inappropriately prescribed patients in our study, physicians generally preferred low dosage. These variables, the HAS-BLED score and age, are rough indicators of bleeding risk. This risk is often the primary reason physicians opt for lower doses. One surprising variable that was found to be significantly higher in the appropriate group was creatinine levels. A possible explanation for this could be that physicians prioritized age (which was also higher in the inappropriate group, although not significantly) over creatinine levels when assessing bleeding risk. Interestingly, the prescribing physicians' tendency for underdosing, particularly in elderly patients, driven by fear of bleeding, seemed to dissipate after an ischemic stroke occurred. This may suggest that physicians are more concerned about bleeding complications than ischemic ones. The reasons behind such a tendency warrant further investigation, as it appears to be a major obstacle to correct dosing.

Furthermore, LAA closure could be another viable option for patients in whom the supposed embolic thrombus is thought to originate from the LAA, and when DOACs did not appear to provide the required protection.[10] Although LAA closure is mainly used in patients with contraindications to long-term anticoagulation, the indications have recently been expanded to include patients who suffered an acute stroke while using DOACs.[11] It may also be considered in patients with LAA morphologic features described as 'malignant LAA', which has been suggested to increase the risk of recurrent stroke.[12] Optimization and more stringent control of vascular risk factors may be beneficial in individuals with a high prevalence of these traits, as demonstrated in some studies using this approach as a component of the 'ABC pathway'.[13]

Finally, catheter ablation, which has been shown to reduce stroke events in anticoagulated AF patients, especially when performed early in the disease course and in patients with a higher CHA_2DS_2-VASc score, may be recommended to lower arrhythmia burden and thus stroke risk.[14]

The finding that mRSs were positively correlated with the presence of parent artery disease in the inappropriate group, but not in the appropriate group, may be explained by the hypothesis that DOACs, when used at appropriate doses, are also effective in preventing strokes in patients with concomitant parent artery disease. Another possible explanation could be that the parent artery disease may have served as an additional etiology in these patients. Lastly, higher mRSs may simply be a detrimental consequence of ineffective anticoagulation. However, further research is needed to confirm this association in the future, as there are no studies to date that have examined this relationship.

While the 2016 Guidelines from the European Society of Cardiology (ESC) on atrial fibrillation management recommended switching to a different anticoagulant if a patient experiences a stroke or a transient ischemic attack while on an anticoagulant, the 2020 update of the same guideline and the 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation made no specific recommendation on this topic. They only reiterated well-known suggestions such as ensuring correct dosage and good adherence to treatment.[6,15,16]

Strengths and limitations

The following are the strengths of our study: (a) treatment regimens were homogeneous as no anticoagulants other than DOACs were included; (b) all medication history was obtained from treating physicians' notes and confirmed with the national medication database for each individual when in doubt; (c) it reflects real-world current practice rather than the unrealistic, highly sterile, and rigid environments of drug trials.

Our study has several limitations. Firstly, it is retrospective in nature and the small population size may have led to a type 2 error. Secondly, the duration of AF in patients was unknown, which could have affected the results due to variable thrombogenicity risk. However, we found no statistical difference in left atrial dimensions, which are usually positively correlated with AF duration, between the study groups (42.2 ± 6.9 vs 44.3 ± 5.1, $P = .1$). Thirdly, our study design did not permit the determination of recurrent stroke incidence despite the use of DOACs. Finally, the absence of follow-up data precluded us from making inferences about the performance of different DOACs.

Conclusions

This study aimed to identify current practice patterns in anticoagulation management after stroke, despite DOAC therapy. It revealed that there is no uniform pattern or consensus among physicians regarding anticoagulation management. Furthermore, it was found that strokes still occur in some patients, even when the treatment is used as intended. The second significant finding was the high frequency of inappropriate prescribing, despite the available evidence demonstrating the detrimental effects of such practice. In light of the finding that recurrent strokes occur with all DOACs without exception, physicians might consider seeking alternative additional treatment options, such as LAA closure and catheter ablation, rather than simply switching to another anticoagulant agent. This approach could be beneficial until more evidence emerges to better determine the optimal management of strokes occurring despite DOAC therapy.

What is known about the subject?

- Recurrent strokes continue to occur even with the use of guideline-recommended non-vitamin K DOAC.
- Data on current and best practices for managing recurrent strokes in patients taking DOAC is limited.
- Inappropriate dosages and residual risk, which persists despite treatment, are believed to play a role.

Does it contribute anything new?

- A lack of uniformity and consensus exists among physicians regarding anticoagulation management.
- Despite adhering to the intended treatment, some patients still experience strokes.
- An alarmingly high number of patients continue to be prescribed inappropriate dosages of DOAC.

Funding

None.

Ethical considerations

In accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, we have completed and adhered to all items on the STROBE checklist for this manuscript.

In this study, possible sex and gender variables were taken into account in accordance with SAGER guidelines.

Full approval was obtained from the local ethics committee (approval number: 2023/01-35). Patient consent statement was waived because of the retrospective nature of the study.

Statement on the use of artificial intelligence

No artificial intelligence was used.

Authors' contributions

H.G. Uzun: conceptualization, data curation, writing-original draft, writing-review and editing. S. Ekinci: conceptualization, data curation. M.A. Şahin: data curation, N.E. Kavuk: data curation, D.F. Baş: conceptualization, writing-review & editing, B. Kılıçaslan: supervision.

Conflicts of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rccl.2024.05.004.

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