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Characteristics of Recurrent Ischemic Stroke in Egyptian Patients with Atrial Fibrillation Receiving Direct Oral Anticoagulants: A Retrospective Study.

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Abstract

Introduction: Atrial fibrillation (AF) is a major cause of ischemic stroke (IS). Direct oral anticoagulants (DOACs) are the standard of care, yet recurrent IS may occur despite therapy. This study aimed to characterize patients with recurrent IS while on DOACs and to explore competing non-cardioembolic mechanisms. **Methods:** A single-center retrospective study of patients with AF who developed recurrent ischemic stroke while on DOACs was conducted between January 2020 and December 2023. We assessed the presence of vascular risk factors, type of index event(s), type of DOACs, pre-stroke CHA2DS2-VASc and Stroke Prognosis Instrument II (SPI-II) scores, stroke severity, and radiological data (brain imaging, carotid vertebrobasilar duplex, and transthoracic echocardiography) to detect the possible underlying stroke mechanism(s).**Results:** Twenty-eight patients (mean age 68.14 ± 10 years; 60.7% female) were included. Most presented with moderate or moderate-to-severe stroke (median NIHSS 8.5). Stroke mechanisms were cardioaortic embolism in 57%, small-artery occlusion in 21%, large-artery atherosclerosis in 7%, and undetermined in 14%. Nearly all patients had elevated CHA2DS2-VASc and SPI-II scores, reflecting a high recurrence risk. **Conclusions:** Recurrent IS in AF patients on DOACs were frequently linked to non-cardioembolic mechanisms in our cohort. Comprehensive evaluation is essential to optimize secondary prevention strategies.

Keywords: Recurrent ischemic stroke, AF, DOACs, stroke mechanism, Egypt, Secondary prevention

Introduction

Atrial fibrillation (AF) increases stroke risk four- to five-fold, accounting for 10–15% of all ischaemic strokes and up to 24% of embolic strokes of undetermined source (1). Although AF-related stroke carries a substantial burden, it represents a potentially preventable risk. Oral anticoagulation (OAC) is the cornerstone of therapy for patients with AF, as recommended by contemporary guidelines (2,3,4), and significantly reduces the risk of ischaemic stroke (IS) (5,6,7). Direct oral anticoagulants (DOACs) are now the standard of care in many settings (8,9), given their more favourable risk–benefit profile compared with warfarin (4,10,11).

Despite this, a subset of patients experiences IS while receiving OAC (12,13,14,15). Reported rates of IS/systemic embolism remain up to 1.5% per year among patients treated with DOACs and up to 2.5% per year in those with prior stroke/transient ischaemic attack (6,16). Emerging evidence indicates that AF patients who sustain IS despite OAC face a high risk of recurrence and mortality (13,14,17,18,19). However, optimal management in this scenario remains uncertain, and current guidelines provide limited direction.

Moreover, while global data confirm ongoing stroke risk despite DOAC therapy, patient characteristics, regional variation in stroke subtypes, and local management practices may substantially influence

recurrence mechanisms and outcomes (13,20). A recent Egyptian study highlighted a high national recurrence burden (21), yet detailed phenotyping of recurrent strokes particularly among the growing population of AF patients treated with DOACs remains scarce. This evidence gap is even more pronounced across North Africa.

Accordingly, we aim to provide granular, region-specific data by comprehensively characterising patients with recurrent IS while on DOAC therapy at a tertiary Egyptian centre. Our objective is to describe this cohort and systematically evaluate the spectrum of underlying stroke mechanisms, thereby informing strategies to optimise secondary prevention in similar clinical contexts.

Methods

Study design, setting, and cohort

We conducted a retrospective analysis of routinely collected clinical data. The cohort comprised consecutive adults (age >18 years) with non-valvular atrial fibrillation (AF) (22) who had a documented index cerebrovascular event transient ischaemic attack (TIA) (23) or ischaemic stroke (IS), and were subsequently admitted with recurrent IS to the ward and stroke unit at Suez Canal University Hospitals between January 2020 and December 2023.

Definitions

Recurrent IS was defined as a new focal neurological deficit arising after a period of clinical stability, lasting >24 hours, with corresponding new ischaemic lesions on brain computed tomography (CT) or magnetic resonance imaging (MRI). Non-valvular AF excluded moderate or severe mitral stenosis and mechanical prosthetic valves. Subjects were required to be receiving an appropriate dose of a direct oral anticoagulant (DOAC) after the index event, adjusted for age, body weight, and creatinine/estimated glomerular filtration rate (16, 24, 25). Treatment choice was determined by the attending physician. Adherence was assessed by structured interviews of patients and/or family members regarding dosing and persistence.

Eligibility criteria

Inclusion: adults with non-valvular AF, prior index TIA or IS, on appropriately dosed DOAC therapy, and admitted with imaging-confirmed recurrent IS within the study period.
Exclusion: haemorrhagic stroke or venous infarction; documented omission of DOAC therapy for ≥7 days before stroke onset (26); valvular AF (moderate/severe mitral stenosis or mechanical valves).

Data collection

We extracted sociodemographic data; detailed characteristics of the index event (TIA or IS, clinical presentation, investigations); DOAC type and dose; and vascular risk factors, including diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), ischaemic heart disease (IHD), and hyperlipidaemia.

For the recurrent IS, we recorded the clinical presentation and calculated the National Institutes of Health Stroke Scale (NIHSS) (27) score, categorised as minor (1–4), moderate (5–15), moderate-to-severe (16–20), or severe (21–42). Pre-stroke CHA_2DS_2-VASc scores (28) were computed, with 0–1 indicating low–moderate thromboembolic risk and ≥2 indicating high risk prior to the index event. The Stroke Prognosis Instrument II (SPI-II) (29, 30) was calculated (pre-stroke) and grouped as low (0–3), medium (4–7), or high (>8) risk.

Neuroimaging and aetiological classification

Radiological patterns of recurrent IS were classified as: (1) carotid territory; (2) branch middle cerebral artery (Br-MCA); (3) total middle cerebral artery (total MCA); (4) anterior cerebral artery (ACA); (5) posterior cerebral artery (PCA); (6) lacunar infarct(s); or (7) multiple territories. Stroke mechanisms were assigned using the Causative Classification of Stroke System (CCS) (31) into: cardioaortic embolism (CE), large-artery atherosclerosis (LAA), small-artery occlusion (SAO), other specified causes (O), or undetermined cause (UND).

All patients underwent extracranial and intracranial Doppler ultrasonography; haemodynamically significant stenosis was defined as ≥50% luminal diameter reduction in the artery supplying the ischaemic territory, according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (32). Transthoracic echocardiography (TTE) assessed cardiac structure and function. At least one brain CT scan was obtained for each subject; MRI was performed when clinically indicated.

Statistical analysis

Analyses were performed using IBM SPSS Statistics, version 20.0 (Armonk, NY: IBM Corp; 2011). Categorical variables are presented as counts and percentages. Continuous variables are

summarised using range (minimum–maximum), mean, standard deviation, median, and interquartile range (IQR).

Results

Baseline characteristics

Twenty-eight subjects met the inclusion criteria; 17 (60.7%) were female. Ages ranged from 38 to 82 years (mean 68.14 years). All had sustained non-valvular AF. Hypertension was the most frequent vascular risk factor (n = 19), followed by diabetes mellitus (n = 7); only three subjects had no additional vascular risk factors (Table 1). The index cerebrovascular event was IS in 16 (57.1%) and TIA in 12 (42.9%). Apixaban was the most commonly prescribed DOAC (67.9%).

Risk scores

All subjects had a pre-stroke CHA_2DS_2-VASc score ≥2. The pre-stroke CHA_2DS_2-VASc score ranged from 2 to 8 (median 5; IQR 4–6; 95% CI for median 4.0–6.0). The SPI-II score ranged from 2 to 10 (median 5; IQR 4–6; 95% CI for median 4.0–6.0), classifying 6 (21.4%; 95% CI 8.3–40.9%) as low risk, 16 (57.1%; 95% CI 37.2–75.5%) as medium risk, and 6 (21.4%; 95% CI 8.3–40.9%) as high risk (Table 1).

Stroke severity at presentation

For the recurrent IS, NIHSS scores ranged from 2 to 20 (median 8.5; IQR 4–14; 95% CI for median 6.0–12.0). Stroke severity distribution was: minor (NIHSS 1–4) in 10 patients (35.7%; 95% CI 18.6–56.0%), moderate (5–15) in 13 (46.4%; 95% CI 27.5–66.1%), and moderate-to-severe (16–20) in 5 (17.9%; 95% CI 6.1–36.9%). No patient had a severe stroke (NIHSS ≥21).

Neurovascular imaging and aetiology

Significant ipsilateral stenosis (intracranial or extracranial) on duplex ultrasonography was present in 6 subjects (21.4%) (Table 2). Transthoracic echocardiography was unremarkable in 14 (50.0%); 11 (39.3%) showed features consistent with ischaemic heart disease, and 3 (10.7%) had congestive heart failure. Middle cerebral artery involvement (branch or total occlusion) was the most common radiological territory (n = 13, 46.4%), followed by lacunar infarcts (n = 8, 28.6%).

Using the Causative Classification of Stroke System (CCS), cardioaortic embolism accounted for 57% of cases. Competing mechanisms were identified in the remainder (Table 2). Four subjects (14.3%) had more than one major potential cause and were classified as stroke of undetermined aetiology.

Discussion

We investigated factors associated with stroke recurrence in a cohort of patients with atrial fibrillation (AF) who sustained ischaemic stroke (IS) despite direct oral anticoagulant (DOAC) therapy. As with most therapies, anticoagulation does not confer absolute protection; a proportion of patients will experience recurrent IS despite apparent adherence. Such “treatment failure” may reflect mechanisms other than non-adherence, including reduced pharmacological efficacy or alternative, non-cardioembolic stroke aetiologies.

IS was the most common index event in our cohort (n = 16), consistent with prior reports (13, 18, 20, 33–35). Accumulating evidence indicates that patients with IS who are already anticoagulated have a higher risk of recurrence than those without prior anticoagulation (15, 18, 36).

Competing mechanisms of recurrence

Multiple underlying mechanisms were identified (Table 2). Cardioaortic embolism (CE) accounted for the largest proportion of recurrent IS despite anticoagulation, in the absence of evidence for under-dosing or alternative primary mechanisms. Six subjects had small-artery occlusion (SAO), two had large-artery atherosclerosis (LAA), and four had more than one potential cause and were classified as stroke of undetermined cause (UND).

Ipsilateral haemodynamically significant stenosis on duplex ultrasonography was present in six subjects (21.4%), contributing to LAA and UND classifications, in keeping with other studies (36–39). The distribution of mechanisms may reflect region-specific vascular risk profiles. The combined burden of LAA and SAO (28.5%), together with a further 14.3% categorised as UND where these mechanisms may be contributory, aligns with the recognised prevalence of intracranial atherosclerosis and hypertensive small-vessel disease in North African and Middle Eastern populations (38, 39). The 21.4% rate of significant ipsilateral stenosis and the 28.6% prevalence of lacunar infarcts suggest that extracranial/intracranial atherosclerotic disease is an important competitor to cardioembolism as a cause of stroke in this region, even among patients with established AF.

Table (1): Demographic data and clinical characteristics

	No. (%)
Age (years)	
Min. – Max.	38.0 – 82.0
Mean ± SD.	68.14 ± 10.03
Median (IQR)	69.50 (63.0 – 75.50)
Gender	
Male	11 (39.3%)
Female	17 (60.7%)
Vascular Risk factors (other than AF)	
Diabetes Mellitus	7 (25.0%)
Hypertension	19 (67.9%)
Ischemic Heart Disease	4 (14.3%)
No other Risk Factors	3 (10.7%)
Index Event	
TIA	12 (42.9%)
Ischemic Stroke	16 (57.1%)
Type of DOAC	
Apixaban	19 (67.9%)
Rivaroxaban	9 (32.1%)
NIHSS Score	
Min. – Max.	2.0 – 20.0
Mean ± SD.	9.04 ± 5.59
Median (IQR)	8.50 (4.0 – 14.0)
Stroke Severity (according to NIHSS)	
Minor stroke	10 (35.7%)
Moderate stroke	13 (46.4%)
Moderate to severe stroke	5 (17.9%)
Severe stroke	0 (0.0%)
Pre-Stroke CHA2DS2-VASc	
Min. – Max.	2.0 – 8.0
Mean ± SD.	4.79 ± 1.40
Median (IQR)	5.0 (4.0 – 6.0)
95% CI for Median	4.0 – 6.0
SPI-II scores	
Min. – Max.	2.0 – 10.0
Mean ± SD.	5.43 ± 2.25
Median (IQR)	5.0 (4.0 – 6.0)
95% CI for Median	4.0 – 6.0
Low Risk	6 (21.4%)
Medium Risk	16 (57.1%)
High Risk	6 (21.4%)

***NIHSS**: National Institute of Health Stroke Scale **SPI-II:** Stroke Prognosis Instrument II **TIA**: transient ischemic attack **DOAC**: Direct oral anticoagulant **AF**: atrial fibrillation **SD**: Standard deviation **IQR**: Interquartile range.*

Table (2): Radiological findings (n = 28)

	No. (%)
CVB Duplex	
Non-significant stenosis	22 (78.6%)
Ipsilateral significant stenosis*	6 (21.4%)
Echocardiography	
Preserved	14 (50.0%)
Ischemic Heart Disease	11 (39.3%)
Congestive Heart Failure	3 (10.7%)
Stroke Mechanism (by CCS)	
Cardioaortic embolism (CE)	16 (57.1%)
Large-artery atherosclerosis	2 (7.1%)
Small-artery occlusion (SAO)	6 (21.4%)
Stroke of undetermined cause	4 (14.3%)
Radiological classification	
Carotid	0 (0.0%)
Branch MCA	9 (32.1%)
Total MCA	4 (14.3%)
ACA	0 (0.0%)
PCA	1 (3.6%)
Lacunar infarct(s)	8 (28.6%)
Multiple territories	6 (21.4%)

***CVB**: Carotid Vertebro Basilar **MCA**: Middle cerebral artery. **ACA**: Anterior cerebral artery **PCA**: posterior cerebral artery. **CCS**: Causative Classification of Stroke System. **SD**: Standard deviation **IQR**: Interquartile range* NASCET ≥50%*

Implications for secondary prevention

These findings reinforce the need for comprehensive diagnostic evaluation in AF patients with IS despite anticoagulation, to identify non-cardioembolic contributors that are less responsive to OAC alone and demand additional targeted prevention. In our setting, optimal management may require not only effective anticoagulation, but also aggressive, goal-directed control of hypertension and other atherosclerotic risk factors, areas that may be under-prioritised when AF is present. A uniform approach to secondary prevention in AF is unlikely to be sufficient; region-adapted guidance that accounts for local epidemiology of competing mechanisms is warranted.

Risk stratification and pharmacogenomics

High pre-stroke SPI-II and CHA_2DS_2-VASc scores in this cohort (78.5% and 100% in medium/high-risk categories, respectively) support the routine use of risk stratification to inform individualised management plans. Genetic variability affecting DOAC pharmacokinetics remains a potential area for exploration (40). Notably, CYP2C9 and VKORC1 variants influence response to vitamin K antagonists rather than DOACs (41).

Therapeutic uncertainty and emerging options

The optimal management of IS occurring during OAC remains uncertain. Recent data suggest that switching between DOACs does not improve outcomes (17–19, 42), while switching to a vitamin K antagonist may increase adverse events (14). Adding antiplatelet therapy to OAC has been associated with worse outcomes (42–44). Novel pharmacological agents, such as factor XIa inhibitors (45), and non-pharmacological strategies, including percutaneous left atrial appendage occlusion, may further advance prevention in selected patients (46, 47).

Strengths and limitations: Strengths include reliance on medical records rather than patient recall, reducing recall bias; comprehensive work-up to assign stroke mechanism; and real-world clinical data that may inform practice. Limitations include the single-centre, small sample; lack of systematic evaluation of therapies other than DOACs; exclusion of patients with uncertain adherence; absence of transoesophageal echocardiography/ advanced imaging in all cases; and no formal assessment of DOAC dosing appropriateness or laboratory markers of anticoagulant effect. We also lacked sufficient data to quantify white-matter disease burden as a potential risk factor for recurrence.

Conclusion

In this descriptive Egyptian cohort with AF, recurrent IS despite DOAC therapy was frequently linked to identifiable non-cardioembolic mechanisms, including small-vessel disease and large-artery atherosclerosis. Comprehensive diagnostic evaluation is therefore essential to uncover competing aetiologies. Optimising secondary prevention likely requires an individualised strategy that addresses all modifiable risk factors beyond anticoagulation alone. Larger, prospective studies are needed to validate these findings and inform tailored management pathways.

Abbreviations: AF, atrial fibrillation; IS, ischaemic stroke; DOACs, direct oral anticoagulants; SPI-II, Stroke Prognosis Instrument II; OAC, oral anticoagulation; TIA, transient ischaemic attack; CT, computed tomography; MRI, magnetic resonance imaging; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; IHD, ischaemic heart disease; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; PCA, posterior cerebral artery; CCS, Causative Classification of Stroke System; CE, cardioaortic embolism; LAA, large-artery atherosclerosis; SAO, small-artery occlusion; UND, stroke of undetermined causes; VKA, vitamin K antagonists.

Declarations

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Consent for publication: Not applicable.

Data availability: Datasets are available from the corresponding author on reasonable request.

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