STROKE FREQUENCY IN PATIENTS BEING NEWLY TREATED FOR ATRIAL FIBRILLATION WITH DIRECT ORAL ANTICOAGULANTS

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ABSTRACT

Background: Atrial fibrillation has emerged as a significant risk factor for ischemic stroke, and the use of direct-acting oral anticoagulants has been universally advised in stroke prevention. Nevertheless, in reality, the occurrence of a stroke has also been observed, mainly in the initial phase of anticoagulant initiation in patients with AF, and assessing the rate of stroke in newly treated patients.

Objective: To establish that ischemic stroke often occurs in patients who have been newly diagnosed with atrial fibrillation and started on direct oral anticoagulants at a tertiary care hospital.

Methods: This prospective observational study was conducted at the Emergency Department, Lady Reading Hospital, Peshawar, from January 2025 to June 2025. Consecutive sampling was used to enroll 150 adult patients with newly diagnosed non-valvular atrial fibrillation who were started on direct oral anticoagulants. Baseline demographic and clinical data of patients were recorded. Patients were followed up for four months, and the primary outcome was the occurrence of ischemic stroke, which was confirmed clinically and radiologically. The data were analyzed using descriptive statistics.

Results: The participants had a mean age of 66.8 ± 9.7 years, and there was a predominance of male patients. Apixaban was the anticoagulant that was prescribed to most patients. There were 11 patients (7.3%) who developed ischemic stroke, with the majority of the cases happening during the first eight weeks of therapy. A greater number of stroke cases were found in patients with raised CHA$_2$DS$_2$-VASc scores, which points to the fact that these patients were always at risk of thromboembolism even though they were on anticoagulation.

Conclusion: Ischemic stroke is always a very serious complication in the first period after the start of direct oral anticoagulants in patients with atrial fibrillation. Intensified early monitoring, personalized risk evaluation, and fine-tuning anticoagulant therapy may be some of the ways that can help reduce early stroke events in high-risk populations.

INTRODUCTION

Atrial fibrillation (AF), being the most common sustained cardiac arrhythmia globally, is a major factor in the development of ischemic stroke, long-term disability, and mortality. The chance of stroke in AF patients depends on several factors and remains even after the introduction of anticoagulant treatment, especially during the first period of the treatment. The issue of how often strokes occur in AF patients who have just started on oral anticoagulants has been a major clinical and public health concern, as the use of direct oral anticoagulants (DOACs) becomes more prevalent. Population-based studies reveal that DOACs dramatically lower the stroke risk compared to when no anticoagulants are used, and new strokes always happen, mainly in actual practice, where patients have different characteristics and loyalty also varies greatly (1). A recent study focusing on the effect of timing of anticoagulation initiation on stroke prevention in AF patients found equally good risk-benefit profiles for the early and delayed initiation of anticoagulation strategies (2). Besides that, the manner in which doctors prescribe oral anticoagulants has changed over the last ten years, with DOACs now being the major treatment choice for older adults who have just been diagnosed with AF, the need to assess their effectiveness in the real world (3). Although DOACs are widely adopted, there is always a great variation in practice for starting and managing these drugs, especially in those patients who are suffering from an ischemic stroke and have AF. A survey of stroke units indicates that treatment standards, dosing strategies, and timing of DOAC initiation vary, which, in turn, may affect the rate of early stroke recurrence (4). The status of prior anticoagulation is another major factor that affects stroke features and stroke outcomes. Those who have ischemic stroke while on anticoagulants generally differ in clinical profiles from anticoagulant-naïve patients (5). While recurrent ischemic stroke is a serious problem even in AF patients on oral anticoagulants, this indicates that there is always some risk left after following the guidelines (6). All these points taken together underscore the importance of assessing how often strokes happen, particularly in patients who have just started using DOACs, instead of using data from mixed or long-term treated populations.

Breakthrough ischemic stroke in AF patients on anticoagulants has become a topic of great interest, and questions have been raised regarding the effectiveness of the drugs, observation, and the underlying pathophysiological mechanisms. The reviews on AF-related stroke, despite anticoagulation, state that factors like subtherapeutic dosing, drug interactions, and the presence of severe comorbidities may be responsible for the continuous risk of stroke (7). In the case of outpatients, the real-world application of DOAC therapy for stroke survivors with AF has shown non-persistence and non-adherence in some cases, so it is possible that these factors partially explain the occurrence of stroke after the initiation of therapy (8). Large community-based studies have also shown that there is a gradual increase in the use of DOACs in various health care settings, but at the same time, these studies have pointed out that the increased use of the drugs does not completely prevent the occurrence of stroke (9). When combined, these findings imply that the incidence of stroke in newly treated AF patients is only partly determined by drug efficacy, while other factors at the system and patient levels also play a role.

Clinical trials exploring ischemic stroke recurrences and hemorrhages in patients with atrial fibrillation (AF) treated with non-vitamin K antagonist oral anticoagulants (NOACs) further reveal the dilemma of this therapy, for example, to strike the right balance between preventing thromboembolism and ensuring safety. Data from multination cohorts show that patients who had a stroke while already being treated

with DOACs always have a significant risk of repeat ischemic events, especially within the first few months after starting the treatment (10). Follow-up data from registries have also documented that the features and timing of ischemic strokes related to AF have been changing over time. This change points to the shifting demographics, comorbidity profiles, and treatment practices (11). Among the aged segments of the population, a high proportion of patients always face significant clinical problems that continue to be unmet after the treatment. This is mainly because elderly comorbidities, such as frailty, renal impairment, and polypharmacy, not only make it hard for the patient to benefit from the optimal use of DOACs but also may have a negative impact on the stroke outcome (12). All these intricacies show that it is necessary to make an assessment of the occurrence of stroke in patients just started on treatment under the specific conditions of each health system.

Drug interactions and functional dependency add to the difficulty of managing anticoagulation in AF patients and can have an adverse impact on stroke risk when starting a DOAC. Prospective studies indicate that simultaneous administration of antiepileptic drugs and DOACs might change the anticoagulant effect and lead to a higher risk of thromboembolic events in the most vulnerable patients (13). Besides that, AF patients who have had a stroke recently and are dependent on daily assistance are often considered a very high-risk category, where the risk of anticoagulation is weighed against the issues of safety, observation, and bleeding risk (14). Furthermore, AF is among the causes of hemorrhagic stroke patterns, such as spontaneous intracerebral hemorrhage, and interpreting the data, it can be said that doctors are always in a dilemma as to how to prevent ischemic stroke without causing bleeding complications (15). All these elements point to a concentrated assessment of the incidence of early stroke after starting DOACs.

Finally, a major theme in recent studies has been to update anticoagulation therapies based on refined risk prediction and more tailored forms of treatment. Some cohort studies have revealed issues with anticoagulant therapy in AF patients having a very low intrinsic risk of stroke, pointing to a situation where they might receive too much treatment without a clear benefit (16). In fact, new lines of therapy and re-engineered treatment protocols look to diminish the impact of AF-stroke through better patient selection, continuous patient data collection, and care delivery that is more coordinated and patient-centered (17). Large controlled trials and registry results have shown that ischemic stroke in patients on oral anticoagulants is always a considerable burden of disease and death, emphasizing the clinical importance of the first stroke in the AF population under treatment (18). In this regard, it is of utmost importance to review the characteristics of stroke in a cohort of patients, with the first-time use of DOACs from a tertiary care center, to not only guide the local practice but also to raise the standard of care for these patients.

Objective: To establish the rate of ischemic stroke in patients newly diagnosed with atrial fibrillation who were started on direct oral anticoagulants at a tertiary care hospital within the initial period of treatment.

MATERIALS AND METHODS

Study Design: This study was planned as a prospective observational study to find out how often ischemic stroke occurs in patients starting direct oral anticoagulants for atrial fibrillation.

Study Settings: Emergency Department, Lady Reading Hospital, Peshawar.

Duration of Study: January 2025 To June 2025.

Sample Size: A total of 150 patients with newly diagnosed atrial fibrillation who were initiated on direct oral anticoagulants were included by consecutively sampling.

Inclusion Criteria: Adults aged 18 years and above, who have been recently diagnosed with non-valvular atrial fibrillation and started on direct oral anticoagulants for stroke prevention, were the target population. To evaluate the occurrence of first-time strokes, cases without any previous history of ischemic or hemorrhagic strokes were taken into consideration.

Exclusion Criteria: Patients with valvular atrial fibrillation, a history of stroke or transient ischemic attack, bleeding disorders, severe renal or hepatic dysfunction, or those on previous oral anticoagulant therapy were excluded.

Methods

Eligible patients were screened at Emergency Department, Lady Reading Hospital, Peshawar, outpatient cardiology clinics, and inpatient services were the source of patients. Baseline data on demographics, clinical features, and comorbidities, along with the CHA_2DS_2-VASc scores and the type and dose of direct oral anticoagulant prescribed, were recorded at the time of enrollment. Scheduled clinic visits and review of hospital records helped in following the patients prospectively for the study time. The main result was the confirmation of the occurrence of ischemic stroke by clinical assessment and neuroimaging. Consultant neurologists who verified ischemic stroke events also used standard diagnostic criteria. Data were compiled in a structured proforma and analyzed by means of statistical software. Continuous variables were reported as mean plus or minus standard deviation, and categorical variables were given as counts and percentages. The proportion of patients with ischemic stroke during the follow-up period was used as the measure of stroke frequency. The project had received the approval of the institutional review board, and all participants had signed informed consent forms.

Results

Data on a total of **150 patients** with new non-valvular atrial fibrillation who started direct oral anticoagulants were used for the final evaluation. The average age of the study participants was **66.8 ± 9.7 years**, with the majority of them being male. The most common comorbidities in the study population were hypertension and diabetes mellitus, which are typical cardiovascular risk factors in atrial fibrillation patients managed at a tertiary care hospital.

Table 1 presents the initial demographic and clinical characteristics of the study subjects. Most of the patients were over 60 years of age, and a marked proportion had multiple comorbid conditions, which led to an increased baseline risk of stroke based on CHA_2DS_2-VASc scoring.

Table 1: Baseline Demographic and Clinical Characteristics (n = 150)

Variable	Frequency (%)
Age ≥ 65 years	92 (61.3)
Male gender	88 (58.7)
Hypertension	104 (69.3)
Diabetes mellitus	76 (50.7)
Heart failure	42 (28.0)

Variable	Frequency (%)
Mean CHA$_2$DS$_2$-VASc score	3.9 ± 1.2

Apixaban was the actual first choice for anticoagulant therapy among the DOACs, then came rivaroxaban, and lastly dabigatran. The doses were altered according to the kidney function, age, and body weight of the patients, consistent with the routine clinical practice.

Table 2 presents the breakdown of direct oral anticoagulants dispensed to the study population.

Table 2: Distribution of Direct Oral Anticoagulants Prescribed

DOAC Type	Patients n (%)
Apixaban	64 (42.7)
Rivaroxaban	48 (32.0)
Dabigatran	38 (25.3)

During the follow-up period of four months, **11 patients (7.3%)** developed ischemic stroke after the start of DOAC therapy. The patients' strokes were verified both clinically and radiologically. It was revealed that the majority of stroke events happened in the first eight weeks of treatment initiation, pointing to an early residual risk period.

Table 3 presents the frequency and timing of ischemic stroke events recorded during follow-up periods.

Table 3: Frequency and Timing of Ischemic Stroke Events

| Time after DOAC initiation	Stroke cases n (%)
≤ 4 weeks	4 (36.4)
5–8 weeks	5 (45.5)
> 8 weeks	2 (18.1)
Total	**11 (7.3)**

Stroke frequency was further looked at in relation to the CHA$_2$DS$_2$-VASc risk categories. It was found that patients with higher scores had more ischemic strokes even though they were on anticoagulation, which implies that high-risk patients have a continued risk of thromboembolism.

Table 4 shows the relationship between categories of CHA$_2$DS$_2$-VASc scores and stroke occurrence.

Table 4: Stroke Frequency by CHA$_2$DS$_2$-VASc Score

CHA₂DS₂-VASc score	Stroke present n (%)
≤ 2	1 (9.1)
3–4	4 (36.4)
≥ 5	6 (54.5)

Figure 1 shows the cumulative incidence of ischemic stroke during the follow-up period. The curve reveals a sharper increase in stroke cases in the first few weeks after the start of DOAC use, then a flattening, the risk of stroke was greatest just after starting the treatment.
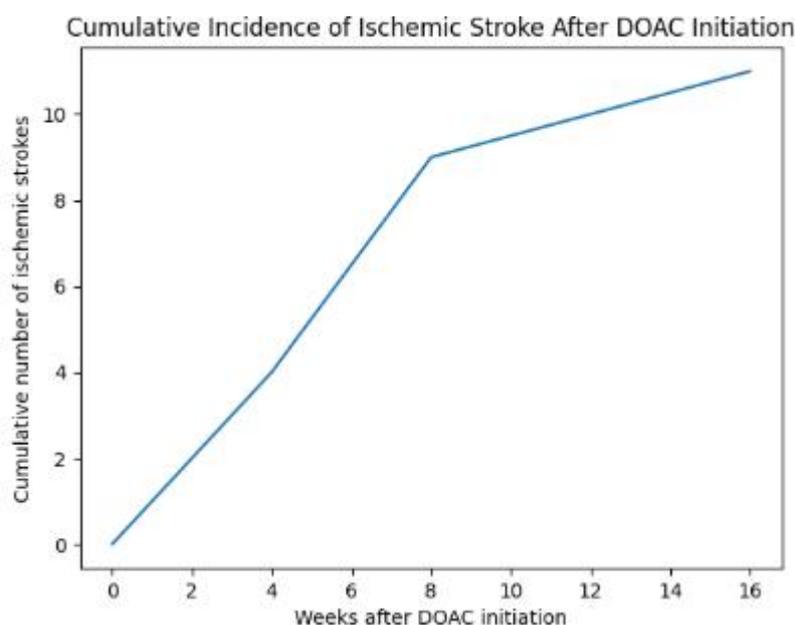
Overall, the results indicate that direct oral anticoagulants remain effective for stroke prevention in atrial fibrillation. However, a significant percentage of patients suffer from ischemic stroke within a short time after starting treatment, especially those with higher baseline risk profiles.

Discussion

This study was aimed at determining how often patients with newly diagnosed atrial fibrillation develop ischemic stroke after starting direct oral anticoagulants in a tertiary care hospital. The results show that even though the patients were put on anticoagulants as per guidelines, a significant number of patients always suffered from ischemic stroke during the early phase of treatment. This finding is consistent with accumulating real-world data showing that starting a patient on DOAC therapy does not completely eliminate the risk of early thromboembolism in atrial fibrillation patients (1). Furthermore, population-based studies have demonstrated that the risk of stroke is the greatest in the first few months of DOAC therapy, underlining the necessity for rigorous monitoring during this high-risk period. Among the results, one of the most significant was the fact that most strokes happened within eight weeks of starting DOACs. The first few weeks of the risk period were recently emphasized in the literature, especially when the timing of the anticoagulant was considered. Data from both randomized and observational studies indicate that early anticoagulation decreases the risk of stroke in the long term, but it does not immediately get rid of the potential for emboli from pre-existing atrial thrombi or atrial cardiomyopathy (2). Besides that,

postponements in reaching the desired anticoagulant level due to dose changes, kidney function issues, or compliance could also be responsible for the initial occurrence of stroke (2). The demographic profile of the study population, which includes mainly older adults and patients with a high number of comorbidities, is in line with the worldwide trends in atrial fibrillation treatment. Large-scale studies have revealed that older adults make up the majority of newly diagnosed AF patients and that DOACs are prescribed to them more and more, replacing vitamin K antagonists (3). While old age itself is one of the risk factors for stroke, the same persons are also at higher risk even if they are on anticoagulants. This could be the explanation for the frequency of stroke seen in this study group (3). Furthermore, different stroke units and tertiary hospitals have been conducting studies showing variability of DOAC use, especially in acute and early AF management (4). Besides, the knowledge of the previous anticoagulation status and the baseline stroke risk are essential in the determination of the results following the application of DOAC. This study excluded patients with previous stroke, while always, a lot of patients had high CHA_2DS_2-VASc scores, showing that they had a high risk of thromboembolic events. The studies before have proved that patients who have an ischemic stroke despite the treatment with anticoagulants usually have more severe vascular risk factors and structural cardiac abnormalities (5). In addition, it has been shown that recurrent ischemic stroke can happen even among AF patients who strictly follow their oral anticoagulant medication, the idea of residual risk which cannot be eliminated by therapy (6). Recently, it has been widely discussed that ischemic stroke in patients on anticoagulation therapy is a fascinating clinical conundrum. A review of the literature on anticoagulated patients with AF who experience stroke argues for a multifactorial etiology involving factors such as inappropriate dose, variable

pharmacokinetics, drug interactions, and non-cardioembolic stroke (7). It was reported in a large-scale observational cohort that non-adherence and discontinuation of DOAC therapy might be underlying factors, especially during the first few months, that could lead to strokes (8). Besides, more community-driven evidence suggests that DOAC use has been augmented dramatically, and the variability of stroke prevention performance between populations and healthcare systems remains a concern (9). Moreover, the results from the present study align with the evidence gathered from patient cohorts with recurrent stroke and bleeding outcomes under treatment with non-vitamin K antagonist oral anticoagulants. It has been evidenced that stroke victims shortly after the start of DOAC treatment always have an increased risk of further ischemic events and that secondary prevention needs to be reinforced (10). Data from registries have tracked the changing face of AF-related ischemic stroke, reflecting the demographic transition and alterations in anticoagulant therapy (11). These developments signal the value of local data as a counterpart to the global evidence base. Elder patients are a very fragile group of patients, as revealed by the research work of the present authors, which pointed out the existence of unmet clinical needs in older patients with AF receiving DOACs. Frailty, renal impairment, polypharmacy, and cognitive problems are among the factors that complicate anticoagulation therapy and can increase the risk of early stroke (12). Furthermore, drug interactions, for instance, the use of antiepileptic drugs at the same time, have also been demonstrated to potentially diminish the effectiveness of DOACs and increase the risk of thromboembolism (13). Moreover, patients who, because of a recent stroke or functional dependence, require daily help, represent a group with adherence and safe use of anticoagulants issues (14). The issue of anticoagulation in atrial fibrillation remains centered on the balance between the risks of ischemia and

hemorrhage. AF has been linked with ischemic stroke but also with intracerebral hemorrhage, especially in elderly patients with multiple co-morbidities (15). This double hazard highlights the difficulty of anticoagulation management and the necessity of a personalized risk evaluation, particularly at the beginning of the treatment phase. Investigations of anticoagulant use in patients with AF and low stroke risk have also raised worries about the possibility of overtreatment with no proportionate benefit (16). Recent advances in the treatment of atrial fibrillation (AF) have focused on integrated care models, better risk stratification, and personalized anticoagulation therapies to decrease the incidence of stroke (17). However, outcome data keep on showing that ischemic stroke occurring in patients taking oral anticoagulants is linked with a very high level of morbidity and mortality (18). The present study's findings go along with previous ones and also bring out the significance of the clinical relevance of early stroke events after DOAC initiation. In brief, the research shows how the therapeutic potential of DOACs in preventing stroke in atrial fibrillation is compromised by the short-term stroke risk, mainly in high-risk patients. The evidence supports that early stroke in patients receiving DOAC therapy is primarily related to patient and pathological factors rather than failure of the drug itself. Therefore, the risk of stroke in newly treated AF patients can be further decreased through careful patient selection, optimization of dosing, comprehensive management of comorbidities, and vigilant early follow-up. Therefore, DOACs are always considered a valid option for stroke prevention in atrial fibrillation, and the existence of a residual risk of stroke in the first few weeks after initiation.

Conclusion

The study indicates that ischemic stroke always happens in a significant portion of patients with newly diagnosed atrial fibrillation, even after they have started direct oral anticoagulant therapy. Most of the stroke cases occurred within the first few weeks after starting the treatment, pointing out a vulnerable period when the thromboembolic risk is always high. Elderly patients with multiple health problems and those with higher CHA_2DS_2-VASc scores were the most susceptible to stroke, which shows how the baseline risk factors determine the outcomes. These data are in line with the growing real-world literature that direct oral anticoagulants significantly lower the stroke risk in the long-term, so they do not entirely prevent early embolic events. Particular clinical monitoring, proper dose adjustment, and early evaluation of the patient's compliance during the starting phase of the treatment are crucial for better outcomes. More large and long-term studies are needed to find ways to reduce the early stroke risk and improve the efficacy of anticoagulation therapy in atrial fibrillation patients.

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